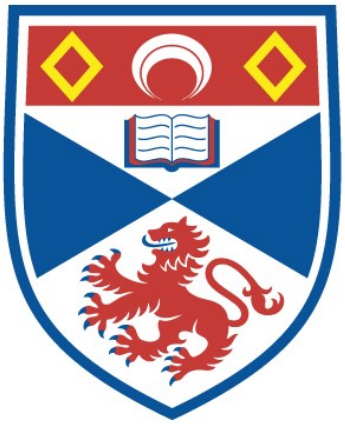
AN IMPROVED SYSTEM OF DAMAGE LIMITATION FOR BETTER RISK CONTROL IN RADIOLOGICAL PROTECTION NEAR ENVIRONMENTAL LEVEL.

Md. Saion Salikin

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1995

AN IMPROVED SYSTEM OF

DAMAGE LIMITATION FOR BETTER RISK CONTROL

IN RADIOLOGICAL PROTECTION

NEAR ENVIRONMENTAL LEVEL

MD.SAION SALIKIN (B.Sc. Hons., MSc)
RADIATION BIOPHYSICS
DEPARTMENT OF PHYSICS AND ASTRONOMY
UNIVERSITY OF ST. ANDREWS.

TL
B748

AN IMPROVED SYSTEM OF

DAMAGE LIMITATION FOR BETTER RISK CONTROL

IN RADIOLOGICAL PROTECTION

NEAR ENVIRONMENTAL LEVEL

by

MD.SAION SALIKIN
B.Sc. Hons (National University of Malaysia)
MSc (Medical Physics, University of Surrey)

A thesis submitted for the degree of Doctor of Philosophy,
University of St. Andrews
St. Andrews, Fife KY16 9SS
United Kingdom

March 1995

Content of the Thesis

Declaration

I, Md. Saion SALIKIN, hereby certify that this thesis, which is approximately 50,000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

This research has been carried out in the Department of Physics and Astronomy in the University of St. Andrews under the supervision of Dr. D.E. Watt.

Date 28th. April 1995 .

Signature of candidate

(Md. Saion SALIKIN)

Certification

I hereby certify that the candidate Md. Saion SALIKIN, has fulfilled the conditions of the Resolution and Regulations appropriate for the Degree of Doctor of Philosophy in the University of St. Andrews and that the candidate is qualified to submit this thesis in application for that degree.

Date.....

Signature of supervisor

.....

Dr. D.E. Watt
Research Supervisor

List of Publications

Watt D E Alkharam A S Child M B Salikin M S 1994 Dose as a Damage Specifier in Radiobiology for Radiation Protection, Letters to the Editor of Radiation Research. *Radiation Research* **139** 249-251.

Salikin M S and Watt D E 1995 Bio-Effectiveness in Nanometre Sites for An Improved System of Risk Control in Radiation Protection, Poster in Association for Radiation Research Annual Meeting (ARR), St. Andrews University 5-8 th. April 1995.

Acknowledgements

I am very grateful to my supervisor, Dr. D.E.Watt, who has been supervising and guiding me by providing the relevant and up-to-date information and for continuous discussion pertinent to my research, during my study as a PhD student . I would also like to extend my gratitude to all my colleagues, especially in the Radiation Biophysics Group, who have been very helpful and cooperative.

I would like to thank to the Government of Malaysia for awarding me a scholarship and other relevant financial assistance for my study.

Finally I would like to express my sincere gratitude to those who have rendered help or given contributions and supports in whatever ways to make this study possible and complete.

Thank you very much.

Dedications

To

MY PARENTS:

HJ. SALIKIN HJ. SALLEH

SITI RUKANAH HJ. YASSIN

MY WIFE:

MAZNAH JASMAN

MY CHILDREN:

ELLY SUZANA

NORLINA

MUHAMAD AZRI

MUHAMAD AFANDI

FARAH DINA

For your moral support, encouragement, patience and understanding.

Abstract

In radiological protection, models are used to assess radiation risk by means of extrapolation from high dose and dose rate to low dose and dose rate. In this thesis five main biophysical models of radiation action have been evaluated, appraised and inter-compared. The five models are lethal and potentially lethal (LPL) by Curtis, pairwise lesion interaction (PLI) by Harder, cellular track structure (CTS) by Katz, hit size effectiveness (HSE) by Bond and Varma and track core (TC) by Watt. Each model has been developed based on certain underlying mechanisms or phenomena, to permit interpretation and prediction on the induction of a specified biological end-point such as cell reproductive death, chromosome aberrations and mutations. Biological systems of interest are, for example, mammalian cells containing deoxyribonucleic acid (DNA). Evidence is mounting that double strand breaks in the DNA are the critical lesions for various biological end points. To proceed with this work the TC model has been chosen.

Cancer induction by ionising radiation is the stochastic effect of prime concern in radiological protection. Cancer induction cannot be avoided entirely but its frequency of occurrence may be reduced to acceptable level by lowering the amount of radiation received. The methods of assessment developed by ICRP, in terms of the cancer risk coefficients, are presented in this thesis.

In the conventional (legal) system of dosimetry, radiation is quantified by the amount of energy absorbed per unit mass of tissue. Quality factors, superseded by radiation weighting factors, are needed to account for the quality dependence on radiation type. As an alternative, a new dosimetry system is proposed here which is based on the mean free path for primary ionisation along particle tracks and the integral fluence generated by the radiation field, whether directly or indirectly ionising radiation. From the study of cellular data, the mean free path for primary ionisation along particle tracks (λ) emerges as a parameter which best unifies biological damage data. Radiation effect is found to depend, not on the energy transferred but to depend mainly on the frequency and spatial correlation of interactions. Maximum effect occurs when λ is equal to λ_o (2 nanometre, nm). The

term 'Absolute Biological Effectiveness' (ABE) is introduced as a parameter which indicates the probability to induce a specified effect, per unit incident fluence. In this endeavour, only direct effects are considered in deriving ABE values for various radiations. However other factors such as indirect effects, inter-track action, repair processes and radiation rate, can be incorporated later if required, in the derivation of ABE. ABE values for photons up to ^{60}Co i.e 1253 keV and neutrons up to 10^5 keV, have been calculated and presented in this thesis.

An attempt has been made to re-express the cancer risk coefficients, derived by ICRP, in the new dosimetry system, in terms of the ABE (Absolute Biological Effectiveness).

The hypothesis put forward in this thesis is that the induction of a specified biological end-point in a biological system due to ionising radiations, is determined not by the amount of energy absorbed per unit mass (dose), but rather by the number of events (ionizations) spatially correlated, along the primary radiation track. Based on this hypothesis, a new unified dosimetry system, independent of radiation type, is proposed. Suggestions are made for possible measuring instruments which have the equivalent response characteristics, namely maximum efficiency of detection for the mean free path λ_o. Success in devising such types of instrument would ensure the practicability of the new dosimetry system, in operational radiological protection.

Table of Contents

List of Tables

List of Figures

List of Abbreviations and Notations

β	Relative speed (velocity/speed of light)
λ	Mean free path for primary ionisation
λ_o	A constant equal to 2 nanometre
Π_γ	Gamma-kill mode survival probability
Π_i	Ion-kill mode survival probability
σ_o	Saturation inactivation cross section
ABE	Absolute biological effectiveness
$^nABE_{tot}$	The absolute biological effectiveness per unit incident neutron fluence
$^nABE_H$	The total absolute biological effectiveness of the hydrogen recoils
$^nABE_O$	The total absolute biological effectiveness of the oxygen recoils
BEIR	Biological Effects of Ionizing Radiation
CB	Chromosome breaks
CRC	Cancer Risk Coefficients
CTS	Cellular Track Structure Model by Katz
D	Absorbed dose
DDREF	Dose and dose rate effectiveness factor
DF	Other modifying factors
DNA	Deoxyribonucleic Acid
DRA	Dual radiation action
dsb	Double strand breaks
D_T	Average absorbed dose in tissue T
E	Effective Dose
E_o	Critical dose
ET	Exchange-type
F or ϕ	Fluence
H	Dose Equivalent (H=NQD)
H_E	Effective Dose Equivalent ($H_E=w_tH$)
HSE	Hit Size Effectiveness Model by Bond and Varma
H_T	Equivalent Dose ($H_T=w_RD_T$)
ICRP	International Commission on Radiological Protection

L	Lethal lesion
LET	Linear energy transfer
LLE	Low level exposure
LPL	Lethal and Potentially Lethal Model by Curtis
LSS	Life Span Study sample
L_∞	Stopping power
m	Target multiplicity
mrem	One thousandth of a rem
N	A modifying factor
NCRP	National Council for Radiation Protection and Measurements
PCC	Premature chromosome condensation
PL	Potentially lethal lesion
PLI	Pairwise Lesion Interaction Model by Harder
Q or QF	Quality factor
rad	Absorbed dose in J kg^{-1}
RBE	Relative biological effectiveness
rem	Roentgen-equivalent-man (DE=D.QF.DF)
RMR	Repair mis-repair model
ssb	Single strand break
Sv	Sievert
TC	Track Core Model by Watt
TLD	Thermoluminescent Dosimeter
UNSCEAR	United Nation Scientific Committee on the Effects of Atomic Radiation
w_R	Radiation weighting factor
w_t	Tissue weighting factor
Z	Atomic number
z^*	Effective charge value

An Improved System of Damage Limitation
for Better Risk Control in Radiological Protection
Near Environmental Levels

CHAPTER ONE
GENERAL INTRODUCTION

1.1. Introduction

In Radiological Protection, the basic objective [1] is to protect individuals, their progeny and mankind as a whole from the deleterious effects of ionising radiation, while still allowing necessary activities that are advantageous but from which radiation exposure might result. Ionizing Radiation is capable of producing detrimental effects [2] to the exposed individuals. The effects are called **somatic** if they become manifest in the exposed individual and **hereditary (genetic)** if they affect off-spring.

For radiological protection, radiation effects [3] can be generally categorised into **deterministic effect** (or non-stochastic) and **stochastic effect**. For deterministic effect, the severity of the effect varies with the dose and a threshold may therefore occur e.g. cataract (lens), erythema, sterility (temporary or permanent). Deterministic effects involve the malfunctioning or loss of function of tissues in organs, mainly due to cell loss and there is a threshold value for the effects. It can be avoided by limiting the doses received to below the threshold dose levels for the effects. For this effect, radiation can damage tissue by killing the cells; or interfering with tissue functions such as regulation of the cellular components, inflammatory reactions which unveil modifications in permeability of cells, natural migration of cells in developing organs, indirect functional effects eg. pituitary gland irradiation, influences the endocrine functions in other tissues. After irradiation most cells continue to function until they attempt to divide.

For stochastic effect the probability of the effect occurring, rather than its severity, is regarded as a function of dose without threshold e.g. cancer induction, hereditary disorders. Stochastic effects express themselves long after the exposure which include for example increased risk of cancer and hereditary disorders. Apparently, there is no threshold dose for the effects. Stochastic effects can not be avoided entirely because they are assumed to occur even at low doses with low frequency i.e. natural background. The effect can be reduced in frequency i.e. its probability, by lowering the dose. There are two types of stochastic effects of concern in radiological protection, namely the induction of cancer in somatic cells; and the induction of hereditary disorder due to alteration of cells in the germinal tissue.

Cell killing in rapidly dividing cells, becomes manifest, a few days or hours after exposure. In slowly dividing cells, death may not occur after months or even years after exposures. The degree of killing increases with dose. In an organ or tissue, if enough cells are killed, its function is impaired. However functional disorders can also result from direct alteration of cellular processes, such as membrane permeability or cell to cell communication. Cell survival curves provide information on the survival fraction of the irradiated cells against radiation dose [4].

Modification of a normal cell, occurs in a process known as neoplastic transformation. Most neoplastic cell transformations do not progress to a cancer. Various agents, including radiation, tobacco smoke, asbestos and other physical agents and chemical carcinogens, can induce the transformation. The effect of the combination of radiation and other agents could be synergistic, additive or antagonistic, and depends among other things on the sequence, timing, frequency, and total duration of exposure to the agents [5]. The transformed cells are capable of unlimited cellular proliferation. However for malignant transformation, namely the ability of the cells to multiply and form tumour when injected into recipient animals, other phenotypic changes can occur as well. Modification of cells of germinal tissue will give rise to hereditary disorder which may manifest in the next generation [6].

In radiological protection, ionizing radiation effects, either stochastic or deterministic, are quantified in the present system of dosimetry, in units of dose or its derivatives such as equivalent dose or effective equivalent dose [7]. Cancer risk is quantified in terms of probability per unit equivalent dose (Sievert Sv) i.e. 10^{-3} Sv^{-1}. The present system of dosimetry, uses the absorbed dose to quantify radiation and the relative biological effectiveness (RBE) and linear energy transfer (LET) to take care of the relative effectiveness i.e. quality of different radiation types [8]. Since 1977, the International Commission on Radiological Protection (ICRP) has used the terms Dose D, Dose Equivalent H (H=NQD where N is a modifying factor, taken to be one, and Q is the quality factor) and Effective Dose Equivalent H_E ($H_E=w_tH$, where w_t is the tissue weighting factor). ICRP made revisions in 1990 and introduced the terms Dose [9], Equivalent Dose H_T in tissue T ($H_T = w_R D_T$. w_R is the radiation weighting factor and D_T is the average absorbed dose in tissue T) and Effective Dose E ($E=w_tH$, where w_t is the tissue weighting factor). The validity of dose as a concept to quantify radiation has been discussed and debated by many authors which include Watt et-al [10], Katz [11][12][13], Bond et-al[14] and Simmons [15]. The quantification of the radiation field by using dose based on relative biological effectiveness (RBE), quality factor (QF) and linear energy transfer (LET), is considered by many to be inappropriate and fundamental changes are required.

In this project an attempt is made to express and quantify the biological effectiveness of ionizing radiation in an improved system of dosimetry which uses the term **absolute biological effectiveness (ABE)**. A biophysical model based on this concept is used to construct an absolute system of radiation effectiveness. For radiological protection purposes the proposed system must be able to quantify the appropriate radiation risk.

1.1.1. Dosimetric Quantities and Principles

Ionising radiation can be categorised into indirectly ionising radiation such as photon (i.e. X-ray and γ-rays) and neutrons; and directly ionising radiations such as electrons, protons, alpha particles and other charged particles [16][17]. Photons will interact with matter (i.e. water) through photo-electric, Compton

scattering and pair production [18][19]. A complex shower of electrons is produced in the matter from these processes. Neutrons will interact with matter through elastic scattering, inelastic scattering, nonelastic scattering, neutron capture or spallation processes. However for interaction between neutrons and water (i.e. tissue), the main interaction products are recoil protons and recoil oxygen. The spectrum of charged particles [20][21] produced from these processes changes with penetration depth through the build up region, reaches equilibrium and falls off under transient equilibrium conditions according to the attenuation of the primary incident radiation. The charged particle equilibrium spectrum is commonly used in dosimetric calculations [22]. The fundamental quantity used in the conventional dosimetry system is the dose which is the amount of energy absorbed per unit mass of the irradiated medium. The radiation field can be described by a few basic terms which includes [23] fluence [24],[25] flux density (fluence rate), energy fluence and energy flux density (energy fluence rate).

1.1.1.1. Absorbed Dose and Equivalent Dose

The absorbed dose D is the quotient of dE by dm, i.e. D=dE/dm, where dE is the mean energy imparted by ionizing radiation to the matter in a volume element and dm is the mass of the matter in that volume element [23]. It is an average quantity and the unit is Jkg^{-1} and 1 Gray(Gy) is equal to 1 Jkg^{-1}. The energy imparted E [26], by ionizing radiation to the matter in a volume is: $E= R_{in} - R_{out} +\Sigma Q$

where

R_{in} is the radiant energy incident on the volume, i.e., the sum of the energies (excluding rest energies) of all those charged and uncharged ionizing particles which enter the volume;

R_{out} is the radiant energy emerging from the volume, i.e., the sum of the energies (excluding rest energies) of all those charged and uncharged ionising particles which leave the volume; and

ΣQ is the sum of all changes (decreases: positive sign, increases: negative sign) of the rest mass energy of nuclei and elementary particles in any nuclear transformations which occur in the volume.

For x-rays and γ-rays the absorbed dose D is given by the following relationship:

$$D= \phi.E_{\gamma}. \Sigma_i (\mu_{en}/\rho)_i \times 1.6\times10^{-13} \text{ Gy}$$

where

ϕ is photon fluence;

E_γ is photon energy in MeV; and

μ_{en}/ρ is the mass energy absorption coefficient (m^2kg^{-1}).

Radiation weighting factors w_R are used to calculate equivalent dose H, from absorbed dose D, by using the following equation:

$$H = \sum w_R.D$$

1.1.1.2. Linear Energy Transfer

The concept of linear energy transfer (LET) was introduced by Zirkle et-al in 1952. ICRU [27] defines LET as follows:

> The linear energy transfer or restricted linear collision stopping power (L_Δ) of charged particles in a medium is the quotient of dE by dl, where dl is the distance traversed by the particle and dE is the mean energy-loss due to collisions with energy transfers less than some specified value Δ.

$L_\Delta = (dE/dl)_\Delta$ and Δ specifies an energy cut-off and not a range cut-off. The energy-loss is sometimes referred to as energy locally imparted.

A medium under irradiation contains a spectrum of charged particle energies, and L_∞ is energy dependent so there is likewise a distribution of L_∞ values characterizing the radiation field. Average value of $\bar{L}_\infty$ can be determined by using two methods namely the track weighted averaging; and dose weighted averaging. It is possible to have two different radiations with the same LET, but giving very different survival fractions [28]. Quality of a radiation refers to features of the spatial distribution of energy transfers, along and within the tracks of particles, that influence the effectiveness of an irradiation in producing change, when other physical factors such as rate, total energy dissipated, fractionation are kept constant.

The LET concept is limited in its application and the limitation of L_∞ in specifying radiations include the followings:

i. Range Effect

> L_∞ does not provide information on the range of the particle which is important to determine whether the particle can traverse a given target

volume or stop in it. If the particle crosses the volume and spends appreciable amount of energy, L_∞ value upon entering and leaving the volume will change significantly.

ii. Delta-rays Production (or primary ionizations)

L_∞ describes the rate of energy loss but not the diameter of the track, along the track. If the diameter of the track depends on the maximum range of delta rays produced in the interaction (i.e.primary ionizations) and with the assumption that the delta rays carry the energy radially outward, so radiation of different types with the same L_∞ could have different track diameter.

iii. Random Variations (Energy Loss Straggling)

L_∞ describes the expectation value (average value) of the rate of energy loss by a charged particle of a given type and energy, but it does not address the random nature of energy losses along the track, which may leave zero energy in a small target volume, or give more energy than predicted on the basis of L_∞.

iv. LET is not single valued for a specified radiation because the same LET can occur on both sides of the Bragg peak.

1.1.1.3. Microdosimetry

Microdosimetry is a science that deals with the spatial, temporal, and energy-spectral distributions of energy imparted in cellular and sub-cellular biological structures, and the relationship of such distributions to biological effects [29]. Rossi H H [30] noted that microdosimetry is dealing with the microscopic distribution of energy in an irradiated material. The differences in response to equal absorbed dose, are assumed to be due to differences in the frequency with which various local energy densities occur within the irradiated material. Microdosimetry seeks to express the quality of radiation in terms of physical parameters to allow quantitative prediction of biological effects for different types of ionising radiations. A few definitions relevant to microdosimetry, have been introduced which include [31][32]:

i. Energy Deposit ε_i

Energy Deposit ε_i is defined as the energy deposited in a single interaction i and given by the following expression:

$$\varepsilon_i = T_{in} - T_{out} + Q_{\Delta m}$$

where

T_{in} is the energy of the incident ionizing particle (exclusive of rest mass);

T_{out} is the sum of the energies of all ionizing particles leaving the interaction (exclusive of rest mass); and

$Q_{\Delta m}$ the changes of the rest mass energy of the atom and all particles involved in the interaction ($Q_{\Delta m} > 0$; decrease of rest mass and $Q_{\Delta m} < 0$; increase of rest mass);

ii. Energy Imparted ε

Energy Imparted ε is the sum of all energy deposit ε_i and may be due to more than one energy deposition event, that is statistically independent particle track.

iii. Specific Energy (Imparted) z

Specific Energy (imparted) z is the quotient of energy imparted ε by mass m i.e. z = ε/m.

iv. Lineal Energy y

Lineal Energy y is the quotient of ε by $\bar{l}$ where ε is the energy imparted to the matter in a volume by a single energy-deposition event, and $\bar{l}$ is the mean chord length in that volume i.e.y= $\varepsilon/\bar{l}$.

v. Five classes of tracks:

Insider; particles originating in the volume may lose their entire energy in the volume;

Starter; particles originating in the volume may leave the volume before losing all their energy;

Stopper; particles originating outside the volume may enter the volume and stop within the volume;

Crosser; particles originating outside the volume may cross the volume, depositing only part of their energy in the volume; and

Glancer; particles 'brush' the wall of the volume so that only δ-rays enter it.

In microdosimetry the specific energy imparted z, is a stochastic replacement for absorbed dose and the lineal energy as a stochastic quantity also conceptually replaces L_∞.

1.1.2. International Commission of Radiation Protection (ICRP) and a System of Dose Limitation

The International Commission on Radiological Protection (ICRP), which has been functioning since 1928, is formulated as an appropriate international body to give general guidance in the field of radiological protection. ICRP [33] has recommended a system of dose limitation, the main features of which are as follows:

i. no practice shall be adopted unless its introduction produces a positive net benefit i.e. justification;

ii. all exposures shall be kept as low as reasonably achievable, economic and social factors being taken into account i.e. optimization; and

iii. the dose equivalent to individuals shall not exceed the limits recommended for the appropriate circumstances i.e. dose limitation.

The basic framework of the Radiological Protection system, recommended by ICRP is intended **to prevent the occurrence of deterministic effects, by keeping doses below the relevant thresholds**, and **to ensure that all reasonable steps are taken to reduce the induction of stochastic effects** [34]. In 1977, ICRP recommended a formal dose limit [35] for whole body irradiation of workers, equal to 50 mSv per year (refer to table 1.1). This limit corresponded to the mortality risk factor for radiation induced cancers (fatal malignancies) of about 10^{-2} per Sv as an average for both sexes at all ages. For members of the public, a mortality risk factor one order of magnitude smaller was deemed appropriate and the recommended dose limit for members of the public was 5 mSv per year. In 1985, the ICRP reconsidered its recommendation on dose limits for members of the public at a meeting in Paris [36] and recommended that the dose limit for members of the public be further reduced to 1 mSv per year. The main reason for the reconsideration is to clarify the applicability of the dose limits for members of the public which was first recommended in 1977. A subsidiary dose limit of 5 mSv per year for some years was permissible provided that the average over a lifetime would, when averaged, not exceed the principle limit of 1 mSv per year.

The latest ICRP recommendation on effective dose limit for workers is equal to 20 mSv per year, averaged over five years (i.e. 100 mSv per 5 years) with the further

provision that the effective dose should not exceed 50 mSv in any single year. The major reason for changes of the ICRP recommendations is the new risk estimates for fatal cancer which are higher than the previous estimates as explained briefly by Clarke [37]. These fatal cancer risk estimates are now proposed by ICRP and contrasted with those adopted by ICRP in 1977, as shown in table 1.3. The data for these estimations are derived mainly from the Japanese survivors. The latest ICRP dose limits recommendations are listed in table 1.2.

Table 1.1: Protection Recommendation [35]

Year	Exposed Population	NCRP		ICRP	
		Limit	Annual Equivalent	Limit	Annual Equivalent
1931-1934	Occupational	0.1 rad/day	~30 rad	0.2 rad/day	~60 rad
1949-1954	Occupational	0.3 rem/week	15 rem	0.3 rem/week	15 rem
1957-1958	Occupational	5(N[1]-18) rem	5 rem (15 rem maximum)	5(N-18) rem	5 rem (15 rem maximum)
	Public	10 rem/30 year	1/3 rem average	5 rem/30 year	170 mrem average
1971	Occupational		5 rem (15 rem maximum)	-	-
	Public		500 mrem (individual) 170 mrem (average)	-	-
1977	Occupational		-	50 mSv/year	50 mSv
	Public		-	5 mSv/yr maximum	5 mSv maximum 0.5 mSv average
1987	Occupational	50 mSv/yr Age x 10 mSv cumulative guidance	50 mSv	-	-
	Public	1 mSv/yr (continuous) : 5 mSv/yr (occasional)	1 mSv (continuous)	-	-
	NIRL, negligible individual risk level	10 μSv /source	5 mSv (occasional)	-	-

[1]N is age in year

Table 1.1: Protection Recommendation [35]

Year	Exposed Population	NCRP		ICRP	
		Limit	Annual Equivalent	Limit	Annual Equivalent
1990	Occupational	Under consideration		20 mSv/yr over 5 years	20 mSv
	Public	Under consideration		1 mSv/yr over 5yr	1 mSv

Table 1.2: The Latest Recommended Dose Limits[2] by ICRP

Application	Dose Limits Occupational	Dose Limits Public
Effective Dose	20 mSv per year averaged over defined periods of 5 years[3]	1 mSv in a year[4]
Annual equivalent dose in: i. the lens of the eyes ii. the skin[5] iii. the hands and feet	 150 mSv 500 mSv 500 mSv	 15 mSv 50 mSv -

[2] The limits apply to the sum of the relevant doses from external exposure in the specified period and the 50 year committed dose (to age 70 years for children) from intakes in the same period.

[3] With the further provision that the effective dose should not exceed 50 mSv in any single year. Additional restrictions apply to the occupational exposure of pregnant women.

[4] In special circumstances, a higher value of effective dose could be allowed in a single year, provided that the average over 5 years does not exceed 1 mSv per year.

[5] The limitation on the effective dose provides sufficient protection for the skin against stochastic effects. An additional limit is needed for localised exposures in order to prevent deterministic effects.

At dose levels received occupationally, the induction of malignant disease (cancer) is likely to be the only significant stochastic effect, except in the developing embryo [38]. The prevention of deterministic effects would be achieved by setting dose limits at sufficiently low values so that no threshold dose would be reached, even following exposure for the whole of a lifetime or for the total period of working life. Radiation levels near those found in the natural environment are considered to be very low level radiation exposure, generally known as a low level exposure (LLE) in which according to Booz and Feinendegen [39] the fraction of exposed cells in a cell population is very much less than one. Arbitrary definitions of low, intermediate and high doses and dose rates by UNSCEAR are given as in table 1.4 (refer UNSCEAR 1986 Report [40] and UNSCEAR 1993 Report).

Table 1.3: Risk Coefficients adopted by ICRP 1990 compared with ICRP 1977.

Organ or Tissue	ICRP 1977	ICRP 1990		
	Fatal Cancer (% Sv^{-1})	Fatal Cancer (% Sv^{-1})	Lethality (%)	Loss of life (y)
Bladder	-	0.30	50	9.8
Bone Surface	0.05	0.05	70	15.0
Breast	0.25	0.20	50	18.2
Colon	-	0.85	55	12.5
Liver	-	0.15	95	15.0
Lung	0.20	0.85	95	13.5
Oesophagus	-	0.30	95	11.5
Ovary	-	0.10	70	16.8
Skin	-	0.02	0.2	15.0
Stomach	-	1.10	90	12.4
Thyroid	0.05	0.08	10	15.0
Red Bone Marrow	0.20	0.50	99	30.9
Remainder	0.50	0.50	71	13.7
SUB-TOTAL	1.25	5.0	-	-
Hereditary defects	0.4*	1.0‡	-	20.0
Total	1.65	←	7.2(weighted)	→

Note:* First two generations only
‡ All generations.

Table 1.4: Definition of low, intermediate and high dose and dose rates [UNSCEAR 1993].

	Doses	Effective Dose Equivalent rates
Low	0.0 - 0.2 Gy	below 0.05 mSv/min
Intermediate	0.2 - 2.0 Gy	0.05 mSv/min - 0.05 Sv/min
High	2.0 - 10.0 Gy	above 0.05 Sv/min
Very or Ultra high	above 10 Gy	-

1.1.3. Biophysical Models and Induction of Radiation Effects

The basic unit of the living organism is the cell. When a cell is irradiated with ionizing radiation, interactions will take place between the cell and radiation [41]. From the physical point of view, radiation interaction with matter involves physical processes such as excitation, ionization, scattering and pair production. However in a biological system the interactions [57] include physical, chemical, bio-chemical and biological stages which cover the time range from 10^{-16} second to future generations (refer to figure 1.1). All energetic charged particles will lose kinetic energy to their environment through coulombic interactions of the charge on the moving particle with the charges on the electrons and nuclei of the matter through which they are passing. Physical processes such as ionizations and excitations can occur in less than 10^{-16} seconds. At low doses, most atoms are unaffected, while a small number are ionised or excited. In about 10^{-12} seconds, physico-chemical process such as induction of free radicals, is expected to take place. In about 10^{-6} seconds, the free radicals are expected to move rapidly to some distance and are expected to be inactivated.

DNA damage can be inflicted by radiation through the following processes:

i. direct ionization (or excitation); or

ii. indirect process, such as free radical induction, set in motion by the transfer of energy to the medium.

Effects of radiation on DNA include the following [127];

i. Single strand (ssb) or double strand breaks (dsb);

ii. Base lesions; and

iii. Cross-links between strands of DNA or between DNA and protein.

DNA physical structure, according to Alberts et-al [42] is shown schematically in figure 1.2. For various radiation-damaged end-points in eukaryotic cells which include cell reproductive death, chromosome aberrations and mutations, the DNA dsb has been implicated as the causative lesion [43][44]. Cell reproductive death is the death of cell when they attempt to divide and can no longer multiply. Repair systems can identify and remove the lesions induced in DNA within a timescale of tens of minutes. Mis-repair events can give rise to point mutations (error-prone), resulted from base sequence changes, or gene deletion or

rearrangements. The important biological structures in the cell namely DNA, can be altered either directly by the disruption caused by ionization or indirectly by free radicals formed and set in motion by transfer of energy to the cell (medium). Damage may occur on the vital parts of the DNA or other important macromolecules of the cells. Direct effects due to radiation which may occur in DNA include double strand breaks (dsb) and single strand break (ssb) in the double stranded-DNA helical structure [45][46]. Other effects such as a variety of recombinational changes as well as cross-links, alteration in sugar and base fractions, base substitution, deletion and so on, may also occur. Chromosome aberrations are also a result of DNA damage. Such changes are believed to be precursor to oncogenic transformations [47] of cells leading to the manifestation of cancers.

The effect of low level radiation on living systems (cells) can be derived and estimated by means of Biophysical Models. Many different biophysical models of radiation action for various biological end-points have been proposed in the literature in an attempt to quantify radiation effects for radiological protection at low doses (refer to chapter two). Effects on human beings exposed to low level radiation, cannot be obtained directly mainly due to statistical limitation. Information or result is obtained from various epidemiological studies such as the atomic bomb survivors, ankylosing spondylitis patients undergoing radiation treatment and uranium miners, which involve exposures at higher level radiation. Effects at low level radiation are estimated by means of biophysical models which guide extrapolation the effect observed at higher level to lower level. Models are important at least for two purposes:

i. to interpret the damage mechanism and to extrapolate the effects obtained from laboratory experiments, normally performed at higher dose in animal studies, to human beings; and

ii. to extrapolate effect from high dose to lower dose near environmental levels and to interpret the damage mechanism.

1.1.4. Cancer Risk Coefficients (CRC)

Liniecki [48] defines the Cancer Risk Coefficients (CRC) as the number of cancer cases per 1000 man-Sv. CRC represents the risk of cancer induction

(stochastic effect) of an individual exposed to ionizing radiation [49]. ICRP Report 60 uses the term **The Nominal Fatality Probability Coefficient** to estimate cancer risks from exposure to radiation, which is defined as the estimated probability of a fatal cancer per unit effective dose. Cancer is the word used to include all forms of malignant disease. Malignant is understood to be descriptive of a tumour that invades and destroys the tissue in which it originates and which can spread to other sites in the body via the bloodstream and lymphatic system. Benign tumour does not produce harmful effects. Tumour is defined as any abnormal growth of tissue or swelling, in or on a part of the body [50]. Tumours may be benign or malignant.

In order to determine the induction of stochastic effects, ICRP has based its recommendations on cancer risk coefficients (CRC). The derivation of CRC is based on risk models which incorporate a great deal of data obtained from:

i. the survivors of the atomic bomb attacks on Hiroshima and Nagasaki in August 1945;

ii. occupational accidental exposures in industries using ionizing radiation;

iii. medical exposures for therapeutic as well as for diagnostic purposes such as ankylosing spondylitis patients; and

iv. occupationally exposed workers such as miners exposed to radon .

All the data are obtained from high dose and dose rate exposures. CRC represent the probabilities of carcinogenesis in the exposed population and are deduced by means of extrapolation from higher dose and dose rate to lower dose and dose rate by using an appropriate risk projection model (chapter three).

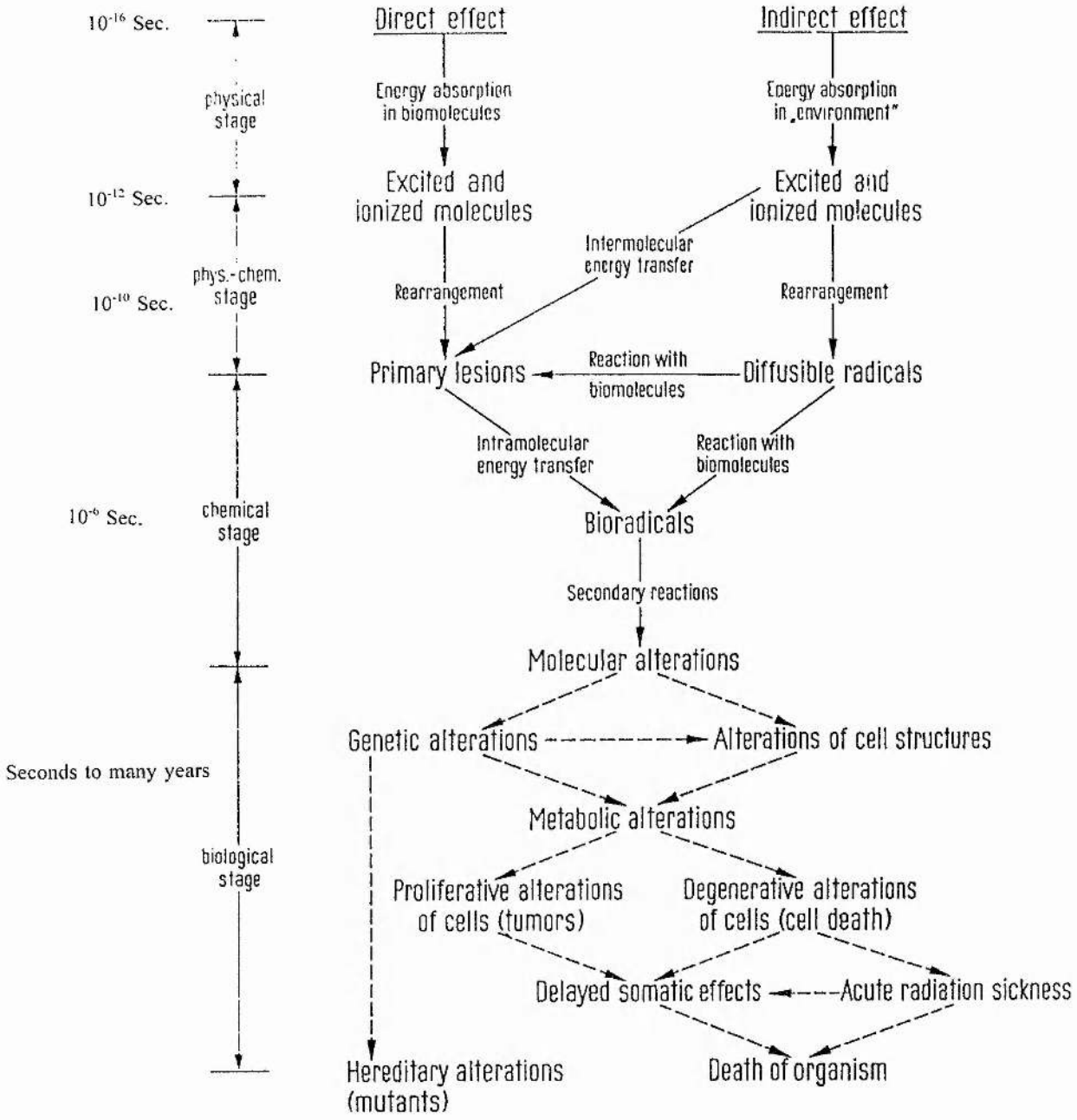
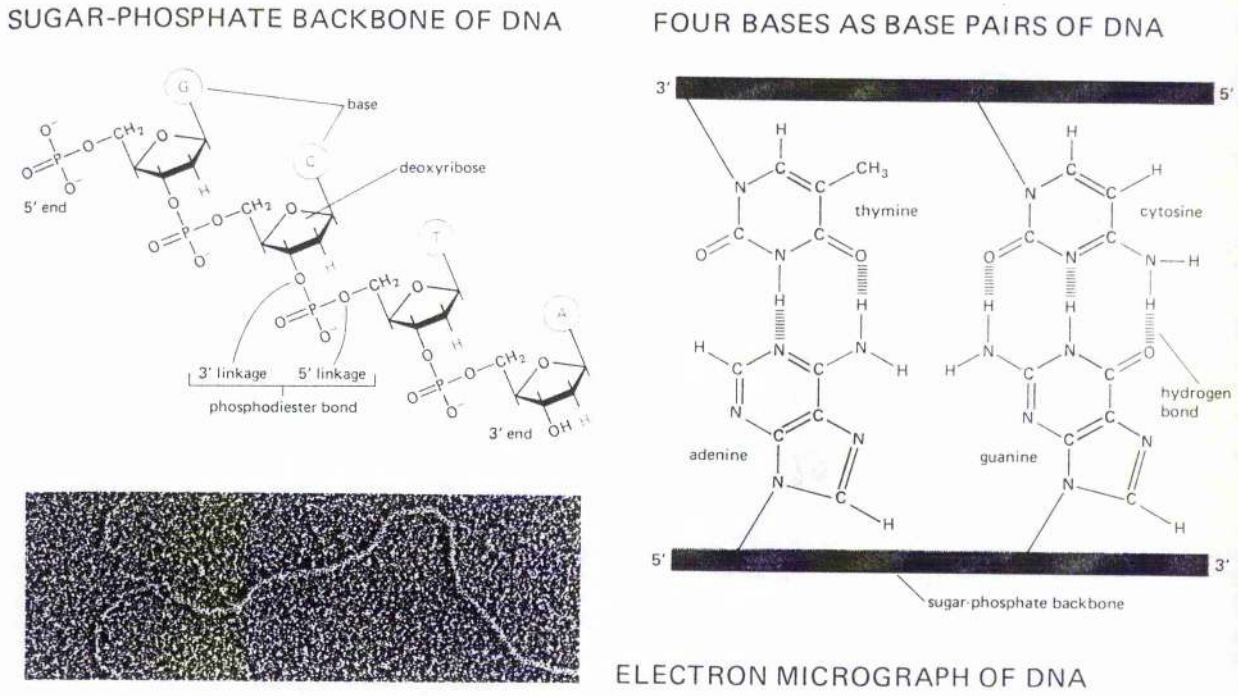


Fig. 1.1: The temporal stages of radiation action. The reaction steps represented by broken lines are affected by metabolic processes [57].



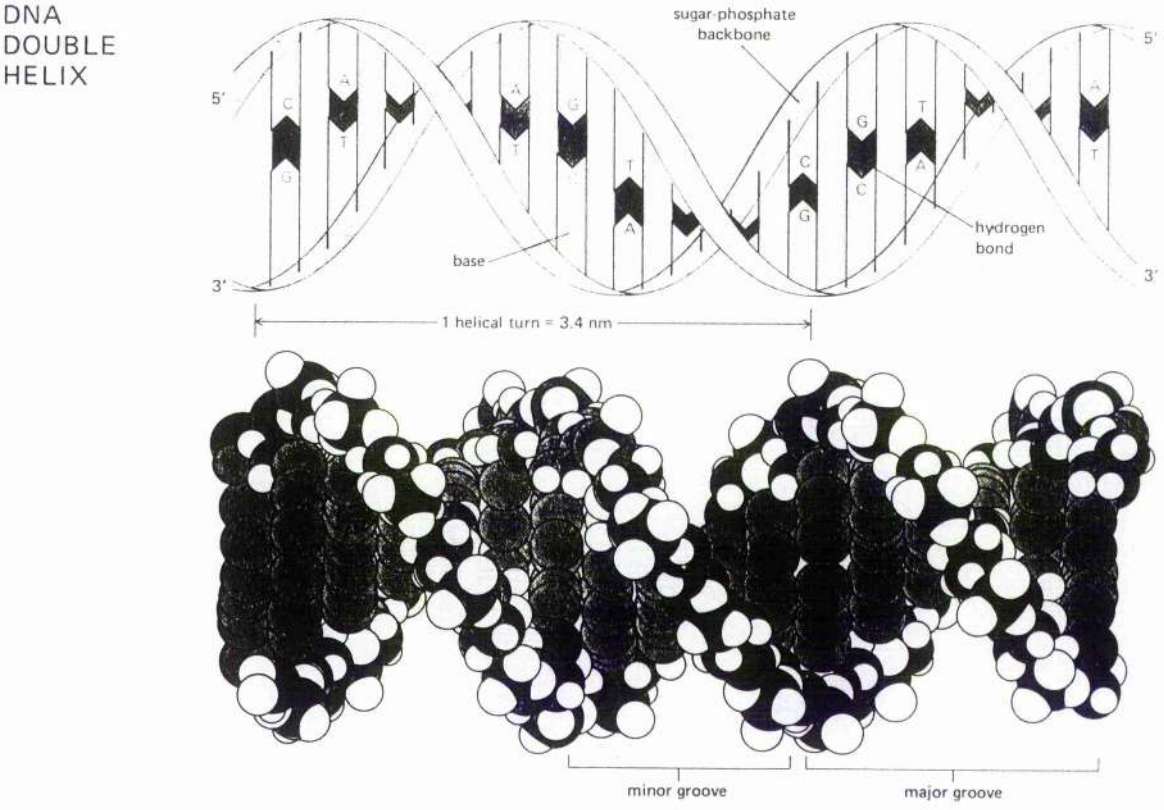


Fig. 1.2: DNA Structure [42]

1.1.5. Present Dosimetry System for Radiological Protection

Before 1991 ICRP recommended the use of the quantity Dose Equivalent H. and Quality Factor Q,which are related by:

$$H = N.Q.D$$

where

N=1 for non-physical modifying factors;

Q is the quality factor of the radiation; and

D is radiation dose.

Absorbed dose D, is used to mean the average dose over a tissue or organ.

Q values are quality weighting factors determined from the LET of the radiation. Values are listed in table 1.5. However in 1991, ICRP [34] considered it necessary to introduce a few changes which include:

i. Radiation weighting factor w_R is used as a weighting factor, on the absorbed dose averaged over a tissue or organ which is related to the quality of radiation (refer to table 1.6 for w_R values). w_R is broadly compatible with Q, which is related to the quantity linear energy transfer (LET). w_R is introduced to make the physical weighting factor on the same format as the tissue weighting factor w_T. However w_R for a specified type and energy of radiation has been selected to be representative of values of the relative biological effectiveness of that radiation in inducing stochastic effects at low doses. The weighted dose is called Equivalent Dose, which is calculated according to the following formula:

$$H_T = \sum_R w_R D_{T,R}$$

where

H_T is the equivalent dose (Sv) in tissue or organ T;

w_R is the radiation weighting factor; and

$D_{T,R}$ is the absorbed dose averaged over the tissue or organ T due to radiation R;

ii. The term Dose Equivalent used in ICRP 26 [33] has been changed to Equivalent Dose in ICRP 60 [34];

iii. The equivalent dose is weighted by the tissue weighting factor w_T, to derive the effective dose E. w_T represents the relative contribution of that organ or tissue to the total detriment resulting from the whole body uniform irradiation (refer to table 1.7,

for w_T values); and

iv. The effective dose E, is the sum of the weighted equivalent doses in all tissues and selected organs of the body and is given by expression:

$$E = \sum_T w_T H_T$$

where

w_T is the weighting factor for tissue or organ T; and

H_T is the equivalent dose in tissue or organ T.

Table 1.5: L_{∞}- Q Relationship

L_{∞} in water (kev/μm)	Q Quality Factor	Radiations
3.5 (and less)	1	β, x, γ etc.
7	2	
23	5	
53	10	α
175 (and above)	20	thermal neutrons C, N, O

Table 1.6: Radiation weighting factors (w_R)

Type and energy range	Radiation weighting factor, w_R
Photon all energies	1
Electrons and muons, all energies	1
Neutrons, energy < 10 keV 10 keV to 100 keV >100 keV to 2 MeV >2 MeV to 20 MeV >20 MeV	5 10 20 10 5
Protons, other than recoil protons, energy > 2 MeV	5
Alpha particles, fission fragments, heavy nuclei	20

Table 1.7: Tissue weighting factors (w_T)

Tissue or organ	Tissue weighting factor, w_T	
	ICRP 60	ICRP 26
Gonads	0.2	0.25
Bone marrow (red)	0.12	0.12
Colon	0.12	n.a*
Lung	0.12	0.12
Stomach	0.12	n.a
Bladder	0.05	n.a
Breast	0.05	0.15
Liver	0.05	n.a
Oesophagus	0.05	n.a
Thyroid	0.05	0.03
Skin	0.01	n.a
Bone surface	0.01	0.03
Remainder	0.05	0.30

* n.a indicates not available.

1.2. Statement of Problems.

1.2.1. Problems with Biophysical Models of Radiation Action

The fundamental understanding of radiation interaction with a biological system to provide interpretations of the radiation effects, which can be used to predict effects at low doses, has not firmly been established. Radiation effects at low levels of radiation cannot be directly measured, mainly due to statistical problems. Therefore to carry out the assessment of risk of radiation effect from low doses, a valid biophysical model of radiation action is required. There are many biophysical models in the literature most of which are meant to be applicable to a specific biological end-point. None of the models are entirely satisfactory. Therefore their ability to predict radiation effects at low doses has to be evaluated.

1.2.2. Problems in Determining CRC

A significant excess for number of cancers occurs in the absorbed dose range from 0.2 to 0.5 Gy is reported by Liniecki [48]. Determination of CRC is derived by means of extrapolation to lower dose, based on certain risk projection models, by utilising all data available up to a certain date. Following the carcinogenic effects of radiation with time after exposure is known as risk projection, which includes extrapolating (projecting) beyond our actual observed experience. The CRC evaluation is subject to review, mainly due to the existence of new or more recent epidemiological and experimental data as well as to new developments in radiological protection as a whole.

1.2.3. Problems with the Currently Accepted Dosimetry System.

In the present dosimetry system the existing problems include the following:

i. Radiation quantity and quality are characterised in terms of absorbed dose and linear energy transfer (LET). Radiation effectiveness is expressed in terms of relative biological effectiveness (RBE). In mammalian systems RBE increases with respect to LET, reaches a maximum value, then decreases. It is not a single valued relationship. It is acknowledged that the LET concept is limited in its application and cannot provide a reliable description of a radiation field (refer to page 5). In Radiological Protection the Quality Factor Q, which is a conservative estimate

arbitrarily related to RBE. is used to indicate radiation quality in order to derive dose equivalent from the formula:

$$H = N.Q.D$$

where N=1 for other modifying factors;

Q is quality factor; and

D is radiation dose.

e.g. The Q for fast neutrons is equal to 20 [51].

In ICRP 60 the Radiation Weighting Factor, w_R is used to derive equivalent dose from the equation:

$H_T = \sum w_R D_{T,R}$;

ii. For the internal dosimetry of Auger-emitting electron capture radionuclides, there are inherent problems in the applications of the concepts of absorbed dose [52]. Radionuclides which decay by electron capture and accompanied by Auger electron cascades or β emission, when incorporated into the molecular structure or mammalian cell nuclei, can cause damage which approaches those for heavy particles [53]. This fact is consistent with the interpretation that electron damage is caused predominantly at the end of the tracks and incorporation of these radionuclides simply ensures that the slowing down fluence of low energy tracks, interacts in the vicinity of the radiosensitive sites. The radiation hazards due to incorporation of the radionuclides is not assessable by conventional dosimetry mainly due to two main reasons namely (a) the complex decay scheme of the radionuclides. For example a single decay of ^{125}I can result in the emission of up to 56 low energy Auger electrons; and (b) Excessive damage beyond that predicted by conventional dosimetry if the radionuclide is incorporated into a sensitive site within the cell structure e.g. the DNA molecule;

iii. Dosimetry of alpha particles [54] ingested through radioactive aerosols cannot be satisfactorily determined;

iv. The quality factor Q, assigned to neutrons having energy in the range of 100 keV to a few MeV is inconsistent with that allocated to heavier ions on the basis of observed effects in mammalian cells; and

v. The present system cannot describe the phenomena of reverse dose rate effects as it predicts smaller effects at low dose rates (due to sub-repair) whereas the opposite (enhanced effect) is sometimes observed.

A new system of dosimetry in terms of Absolute Biological Effectiveness (ABE), is proposed here. The degree of success in overcoming many of the current problems will be explored in chapter four. The concept put forward in the new system is not the energy absorbed per unit mass but the frequency and spatial correlation of track interactions with the DNA segments at risk, in the irradiated system.

1.3. Objectives and Content

The main objectives of the research described here are;

a. To carry out a detailed evaluation and critical appraisal of the main biophysical models of radiation action with particular reference to the primary track model under development at St. Andrews' University;

b. To re-assess and correlate cancer risk coefficients, utilising all information available at the present time, in terms of the currently accepted model and for the St. Andrews' primary track model of radiation damage; and

c. To propose a new system of dosimetry, in terms of Absolute Biological Effectiveness (ABE).

Detailed aspects of the work are discussed in the chapters enlisted. In chapter two, five main biophysical models of radiation action will be evaluated and critically appraised and the results will be presented. In chapter three the available information on cancer risk coefficients will be presented. The currently accepted system of dosimetry will be explained. The link between the cancer risk coefficient and dose limitation will be indicated. The deficiencies of current system are indicated which lead to the proposed new system of dosimetry. In chapter four, the principle and derivation of quantities used in the proposed new system will be described and discussed. In chapter five the conclusions, discussion and recommendations for future work will be presented.

1.4. Scope of the project

The topic of this project is **An Improved System of Damage Limitation for Better Risk Control in Radiological Protection Near Environmental Level**. Argument is presented to justify for an alternative system to the present system of dosimetry. The new system utilises biophysical quantities which can specify the absolute biological effect of the radiation field. In this initial investigation, the study is constrained to environmental levels of radiation where single track effects prevail.

CHAPTER TWO

BIOPHYSICAL MODELS, INTERPRETATION AND EVALUATION

2.1. General

A biophysical model of radiation damage is an analytical tool, based on an understanding of radiation interaction with matter and of the biology of the cell. A good model should permit interpretation of the mechanism of radiation action and should be in a mathematical formalism which will enable extrapolation of data measured at high doses to predict effects at low doses. The major aim of developing a good model is to predict radiation effect at low doses from observations at higher doses. There are many biophysical models found and reported in the literature, however only five main biophysical models will be appraised and evaluated in this chapter.

The mammalian cell is considered as the basic unit of the biological system. The cell consists among other things, of a cytoplasm and the cell nucleus. The cell nucleus has a complex structure covered by a nuclear membrane and it contains deoxyribonucleic acid (DNA) and other components [55]. DNA is a key component (refer to figure 1.2). The time range between the irradiation and the manifestation of effects, varies from 10^{-15} second to next generations (refer to figure 1.1). In biophysical modelling, there has been some convergence of ideas on a few points such as the nature of the biological target, the DNA in the cell nucleus; the nature of important damage, DNA double strand break (dsb); and the requirement to create a crucial lesion. However there is no concession yet on the mathematical form of the dose effect and on the nature of the crucial lesion.

The double strand break (dsb), is now considered to be the crucial lesion. It could possibly occur due to intra-track of one radiation track, as well as inter-track of two radiation tracks. The single strand break (ssb) is considered only as a sub-effective lesion which is easily repaired by the available repair mechanism. Experimental evidence shows that the probability of the final radiation effect depends on a number of modifying factors such as repair, repopulation and cell cycle stage [46].

The main objectives in modelling of radiation action. include the following:

i. to assess the risk of biological effect from low doses of radiation.
ii. to link between physics and biology in studying the radiation effect in a biological system:
iii. to investigate basic mechanisms of radiation action; and
iv. to suggest new experiments to test hypotheses predicted by the biophysical model in various applications such as radiation therapy and assessment of risk.

In the assessment of biological effect from low doses of radiation, data are only readily available from people exposed to larger doses such as for medical reasons or atomic bomb survivors. Statistical limitation prevents us from obtaining actual experimental data of radiation effects at lower doses and dose rates, where people and radiation workers are exposed. Assessment of biological effect at lower doses and dose rates, which is very important for radiation protection, can be extrapolated from higher doses and dose rates by means of a biophysical model of radiation action.

The study of cell proliferative death, the dependence of survival on radiation quantity and quality, remains the principle tool for researchers in radiation biology. However the shortcomings of this study applicable to mammalian cells are, for example, a wide range of cell sensitivity and a limited division potential of the cell. These, to some extent, limits our ability to interpret and understand entirely the action of radiation at the organismic level. Clonogenic survival is defined as the ability of a single cell to proliferate reproductively to form a colony of cells. This method of colony counting has been widely used for clonogenic survival studies on bacteria, virus, yeast and other lower organisms. However it is only since the late 1950s that the method, pioneered by Puck and Marcus [56] has been applied to mammalian cell lines. Among the common mammalian cell lines (mostly are immortal or transformed cells) are HeLa cells, derived from a human cervical cancer; V79 cells, derived from hamster lung; CHO cells, derived from hamster ovary; 9L cells, derived from rat gliosarcoma; and T1 cells, derived from a human kidney. Due to recent developments in cell culturing methods, it is now possible to

undertake survival analysis in vitro from fresh explants of normal and tumour tissue, as well as non-immortal lines that divide for only a few tens of generations. The criterion of clonogenic survivability is usually taken as the production of 50 or more cells at the minimum after 10 to 20 days from seeding.

2.2. General Types of Biophysical Models

2.2.1. Hit and Target Model

In this model [57], a biological cell or system is assumed to consist of targets which must be hit in order to inactivate the cell or the system. The probability of inactivation generally is assumed to follow the Poisson statistical law. Depending on the assumed number of hits and targets involved, the model can be further categorized into single hit single target, single hit multi-target, multi-hit single target and multi-hit multi-target.

2.2.1.1. Single Hit Single Target

In this particular case, one hit is required to inactivate the target and the cell is assumed to have one target. The survival fraction $F_{1,1}$, of a cell population irradiated with radiation is given by $F_{1,1}$= exp (-h), where h is the mean number of hits per target.

2.2.1.2. Single Hit Multi-Target

For single hit multi-target action the cell is assumed to consist of many targets and a single hit is required to inactivate a target. However many targets have to be inactivated in order to inactivate the cell. Survival fraction for single hit and multi-target where m is the number of targets, is given by $F_{1,m}=[1-(1-\exp(-h))^m]$.

2.2.1.3. Multi-Hit Multi-Target

For multi-hit (n) and multi-target (m) the cell is assumed to consist of many targets and each target requires several hits to inactivate the cell. The survival fraction of the irradiated cell population is given by: $F_{n,m}= 1-(1-F_{n,1})^m$

where $F_{n,1}=\exp(-h)\cdot\sum_{r=0}^{n-1}\frac{h^r}{r!}$

n is the number of hits;

m is the number of targets; and

h is the mean number of hits per target.

2.2.2. Two Component Models

In two component models, the radiation action is divided into two components namely low and high linear energy transfer (LET). For the high LET component, the response is assumed to follow single hit, single target characteristics. This is considered to be an irreversible mechanism. For the low LET component, the response is expected to follow single hit, multi-target characteristics. It is considered to be a reversible mechanism which could be influenced by various factors such as repair and oxygenation. Examples of two component models are models by Todd [58], Wideroe [59] and Katz (see Section 2.4.3).

2.2.3. Dual Radiation Action Model

In the dual radiation action model, two separate modes of radiation action are assumed to take place to produce primary lesions namely;

i. linear component of local energy concentration or dose;

It is due to intra-track action, which is attributable to the lesions produced along the individual particle track; and

ii. quadratic component of dose;

It is due to inter-track action, which is attributable to the lesions produced by means of separate charged particle tracks.

The overall effect of radiation in this model is assumed to be dependent on linear dose and quadratic dose. Examples of dual radiation action model are models by Rossi-Kellerer [72], Neary [60] and Chadwick-Leenhouts [71].

2.3. Review of Biophysical Modelling

At the beginning (i.e. contemporary with Lea [62]), the central focus on biophysical modelling was on hit and target theory [61]. Then it was followed by dual radiation action (linear quadratic), two component and microdosimetric concepts. Recent developments in biophysical modelling deal with nanometre dimensions which are of the same order of magnitude as the dimensions of a DNA double

stranded segment, and based on the hypothesis that the DNA double strand is the critical target for radiation effect. In the future it is expected that the challenge is to determine, from molecular biology, how many affected targets i.e. DNA dsb and indeed, possibly the type of dsb, which relates directly to the effects.

Models of radiation action, proposed and formulated for various biological end-points by different authors in the literature, employ different approaches and concepts. Some authors extend a combination of concepts proposed by earlier authors. Radiation is believed to incur in localised damage in sub-cellular sites. Such damage sites are sometimes called lesions or sub-lesions, depending on their categorization, in the critical site of the irradiated cells. Various steps in the supposedly multi-stage process, starting from the physical process, through chemistry, biochemistry and biological processes, are systematically analyzed and modelled and are eventually formulated into a mathematical presentation. The processes which have been taken into account in the literature are:

i. Lesions or sub-lesions, their rate of formation and total (integral) lesions;
ii. Interaction between lesions or sub-lesions induced by inter-track and intra-track action; and
iii. Removal or repair of lesions or sub-lesions mainly due to repair processes or cell division.

Among the first models reported in the literature is the hit and target model by Lea [62]. Conceptually a cell or the sensitive part of the cell, consists of a target (or targets) which must be hit by radiation before the cell is inactivated. The number of hits for each target can be single (single-hit) or multiple (multi-hits). Generic variations of this model include single-hit single-target, single-hit multi-target, multi-hit multi-target and multi-hit, single-target versions.

Lesion formation and its removal or repair has also been used as a basis for modelling of radiation damage. For example the repair mis-repair model (RMR) by Tobias et-al [82], lethal and potentially lethal model by Curtis [78] and the cybernetic model by Kappos et-al [63]. The saturable model by Goodhead [64] also applies the same concept.

Barendsen [65][66] proposed that the surviving fraction (SF) of mammalian cells can be described adequately by a linear quadratic function of the dose represented by $SF=\exp-(\alpha D+\beta D^2)$. The parameters α and β can be interpreted as representing induction of damage from single track and from two independent tracks of ionising particles. Curtis [67] derived his lethal and potentially lethal (LPL) model based on two types of lesions; reparable and irreparable, which are linked to DNA dsb of different severity. Leenhouts and Chadwick [68] proposed, from a molecular theory of radiation biology, that the dose response for the induction of DNA dsb is linear quadratic. The linear coefficient is dependent on the radiation type and the quadratic coefficient is dependent on the dose rate. The model predicts that there will be an interaction between two radiations when applied together or in immediate sequence. Zaider [69] elaborated on the concept of dual radiation action (DRA) in biophysical modelling. DRA refers to mechanisms of radiation effects which can be described in terms of the pairwise interaction of sub-lesions produced from cellular alterations. Examples are the formation of DNA dsb from two single strand breaks (ssb) or Exchange-type (ET) chromosome aberrations from simple chromosome breaks (CB).

Goodhead [70] has proposed that the models of radiation action may be broadly divided into two categories of model: phenomenological and mechanistic, although there is often overlap. Phenomenological models seek a parameterized mathematical description which fits the range of data of interest without the specific need to be related to the actual physical mechanism of radiation action. Mechanistic models seek a conceptual, parameterized description based on realistic assumptions related to basic mechanisms of radiation action.

The structure of charged particle tracks has also been intimately related to modelling. Katz [96] for example derived his two component model. In this thesis it is called the 'Cellular Track Structure' model, based on the track structure of heavy ions and the effects of the delta-ray distribution in dose. The model has generalised factors as he applied it to radiation detectors, nuclear emulsion and cellular radiobiology. Watt et-al [114] developed a phenomenological model based

on observation of the dependence of effect cross-sections on the track core. In this thesis it is called the 'Track Core' (TC) model. It includes direct and indirect effects (radical) along single tracks. Another approach is based on lesions or sub-lesions interaction such as the molecular model by Chadwick and Leenhouts [71], and its dual radiation action by Rossi and Kellerer [72][73] .

Paretzke [74] classifies all radiation damage models into two namely Dosimetric and Track Related Biophysical Models. Dosimetric models basically incorporate explanations from dosimetric point of views such as macroscopic dose, microscopic dose, linear energy transfer, degradation spectrum and radial dose. Whereas track related models incorporate explanations based on various interaction patterns along the track structure of radiation in the medium. Examples are nearest-neighbour analysis, activation-centred neighbourhood analysis, track entities, cluster formation and cluster association.

The microdosimetry approach, which basically takes the geometrical and spatial distribution of energy dissipation into consideration to some extent, has played its role in the modelling of radiation damage. Bond and Varma's hit-size effectiveness (HSE) model [107] applies microdosimetry concepts to predict pink mutations in tradescantia. Although it has had only limited success, it offers a different approach to biophysical modelling and is one of the few which specifically exploits microdosimetry per se.

Varma et-al [75] have proposed to classify models into two basic categories namely mechanistic models and phenomenological of empirical models. Models such as dual radiation action by Kellerer and Rossi; more generalised theory of dual radiation action; Goodhead's threshold model; Curtis LPL damage model; and Tobias' repair mis-repair model (RMR), are examples of mechanistic models. Examples of phenomenological of empirical models are gamma ray theory of RBE of Katz and hit size effectiveness approach (HSEA) of Bond and Varma. In mechanistic models a certain mode of interaction of radiation with biological systems is postulated, on the basis of which a biophysical model for prediction of biological effects is developed. The number of identifiable parameters to which a

physical significance can be attached must be minimum. However if the number of the parameters becomes too large, these approaches lose their significance as being mechanistic and become difficult to validate statistically. Phenomenological models which utilize sets of existing data on biological end-points in one or more systems, are used to develop a methodology by which a predictive response function may be obtained.

In the DSB Model by Ostashevsky [76], DNA double strand breaks (dsb) are considered as the only important radiation induced lesions, and the recovery kinetics for split dose, multi-fractionated and continuous irradiations are considered with the assumption that a cooperative type of dsb repair takes place. In cooperative repair all dsb in the same DNA molecule are repaired simultaneously whereas in non-cooperative repair each dsb is repaired independently. For the latter the repair process may take a different mean time.

Hall [77] noted the importance of the premature chromosome condensation (PCC) technique which can be used to assess the number of initial chromosome breaks without waiting until the next mitosis of the cell. The data may be used by the modellers to establish a relationship between the initial strand breaks and cell lethality.

In St. Andrews, the basic approach used in model development was first to extract effect cross-section from a wide range of available published survival data for inactivation and chromosome aberrations, for many different radiation types and to explore their correlation against various physical track structure parameters. By this means the importance of the mean free path for primary ionisation emerged and the role of the 2 nm spacing in the DNA was identified. Thus the DNA dsb was identified as the fundamentally critical lesion for single tracks. Its induction efficiency is determined by λ. Will the approaches and concepts used in modelling achieve the desired goals? Current thinking is that the process which gives rise to the various biological end points such as cellular inactivation, cell mutation, chromosome aberration, neoplastic transformation etc, is a multi-stage process initiated by the formation of lesions in the DNA and ameliorated by possible repair

mechanisms (enzymatic) operating in the cell. The probability of the subsequent biological end-point occurring may be determined by chance.

2.4. Evaluation and Critical Appraisal of Models

In this work the following five main biophysical models of radiation action will be evaluated in more detail and critically appraised:

i. Lethal and Potentially Lethal (LPL) Model (Curtis);
ii. Pairwise Lesion Interaction (PLI) Model (Harder);
iii. Cellular Track Structure (CTS) Model (Katz);
iv. Hit Size Effectiveness (HSE) Model (Bond and Varma); and
v. Track Core (TC) Model (Watt).

Evaluation and critical appraisal of a biophysical model, should be linked to the expected performance of a particular biophysical model. As a prerequisite, the model should be identified and be explained in brief. After understanding the basic principle and its survival equation, an overall appraisal on a particular model is carried out. If available, the testing of the model by the author is included in brief. A comparison of the models will be shown to indicate similarities and differences in the results or prediction of the models. The following criteria if applicable, are used in the test and comparison of model:

i. Initial slope;
ii. Final slope;
iii. Number of parameters and their meaning; and
iv. Basis of the model.

2.4.1. Lethal and Potentially Lethal (LPL) Model (Curtis)

2.4.1.1. Introduction

The Lethal and Potentially Lethal Damage (LPL) model by Curtis [78] identifies the main types of radiation damage as lethal (L) and potentially lethal (PL) lesions. This model can be described under the heading of lesion interaction [79][80] and the model is derived by merging certain features of the cybernetic model [63] and the repair misrepair model (RMR) [81]. L lesions cannot be repaired correctly whereas a potentially lethal (PL) lesion can be repaired correctly (viable). PL lesion can become lethal by interacting with another PL lesion (binary misrepair) or PL lesion can be fixed to become a L lesion. The rate of production of L lesions and their repair rates are taken into consideration in deducing the mathematical expression for this model. In deriving the survival curve, a Poisson distribution is assumed to apply and it is related with the number of PL and L lesions.

2.4.1.2. Basic principles

The LPL model by Curtis, combines various concepts used in biophysical modelling of radiation action which includes lesion interaction, irreparable lesions caused by single tracks, linear lesion fixation, lesion repair and binary mis-repair. LPL model identifies the lesions as DNA double strand breaks with different severity, which can be divided into two [82], namely;

i. Potentially Lethal Lesion (PL)

   PL lesion is a potentially lethal lesion which is less severe and can be caused by less energy deposited locally. It has the possibility of being correctly repaired presumably by cellular enzymatic process. A PL lesion can interact with another PL lesion to form a lethal lesion L and the interaction is called binary misrepair. A PL lesion may also be fixed to become a lethal lesion for example by the cell moving into or through some critical phase of its cycle. Curtis calls the process 'linear fixation'.

ii. Lethal Lesion (L)

   L lesions are lethal and considered more severe than PL lesions. To produce an L lesion, a larger deposition of energy is required, locally. This type of lesion cannot be repaired correctly (irreparable).

Two processes compete for depletion of the PL lesions namely correct repair process and mis-repair process. PL lesions can also be fixed to become L lesions by means of a fixation process. The role of PL repair rate and repair time are important in this model which are significant in the survival equation [83][84][85].

There are repair provisions for lethal (L) and PL lesions, namely:

a. for the production rate of PL lesions:

$$\frac{d\overline{\eta}_{PL}}{dt} = \eta_{PL}\dot{D} - \epsilon_{PL}\overline{\eta}_{PL} - \epsilon_{2PL}\overline{\eta}^{2}_{PL}$$

where $\dot{D}$ ≡ the dose rate

$\eta_{PL}\dot{D}$ ≡ PL lesion production rate

$\epsilon_{PL}\overline{\eta}_{PL}$ ≡ due to repair

$\epsilon_{2PL}\overline{\eta}^{2}_{PL}$ ≡ due to the production of mis-repaired lesions (loss)

b. The rate of change of PL lesions is:

$$\frac{d\overline{\eta}_{PL}(t)}{dt} = - \epsilon_{PL}\overline{\eta}_{PL}(t) - \epsilon_{2PL}\overline{\eta}^{2}_{PL}(t)$$

where $\epsilon_{PL}\overline{\eta}_{PL}(t)$ is due to repair of PL lesion; and

$\eta_{2PL}\overline{\epsilon}^{2}_{PL}$ is due to the mis-repaired lesions.

2.4.1.3. Survival equation

For cell survival (SF),

$$SF=\exp\left[-(\eta_{L}D+\eta_{PL}D) + \epsilon \ln\left[1+\frac{\eta_{PL}D}{\epsilon}\left[1-\exp(-\epsilon_{PL}t_{r})\right]\right]\right]$$

with ε is equal to the ratio between rate per unit time of correct repair and rate per unit time of binary misrepair for PL lesions, given by: $\epsilon = \frac{\epsilon_{PL}}{\epsilon_{2PL}}$

where

η_{l} is the rate of production of lethal lesion per unit Absorbed Dose;

η_{Pl} is the rate of production of potentially lethal lesions per unit Absorbed Dose;

D is the Absorbed Dose;

ε_{PL} is the rate per unit time of correct repair for potentially lethal lesions;

ε_{2PL} is the rate per unit time of binary misrepair for potentially lethal lesions; and

t_r is the available repair time i.e. t_r=t-(irradiation time T).

2.4.1.4. Model Appraisal

Dose is used to quantify radiation in this model. The basis for Curtis' model is the interaction between lesions and there are two categories of lesion introduced in the model to distinguish between reparable and irreparable lesions. Although a specific radiosensitive site is not specified, it is implicit that the lesions are in the DNA molecule. Different degrees of severity are used to indicate the type of damage by the radiation action such as single strand break or double strand break. Inter-track effects (binary misrepair) as well as intra-track (irreparable) effects are taken into account.

2.4.1.5. Testing Curtis' model

Curtis tested his model [84], by using data listed in table 2.1, namely Ne ions, alpha particles at different LET and x-rays data from:

i. Barendsen et-al 1960 for kidney cells of human origin [86];

ii. Raju and Jett 1974 for human kidney cells (T-1) [87]; and

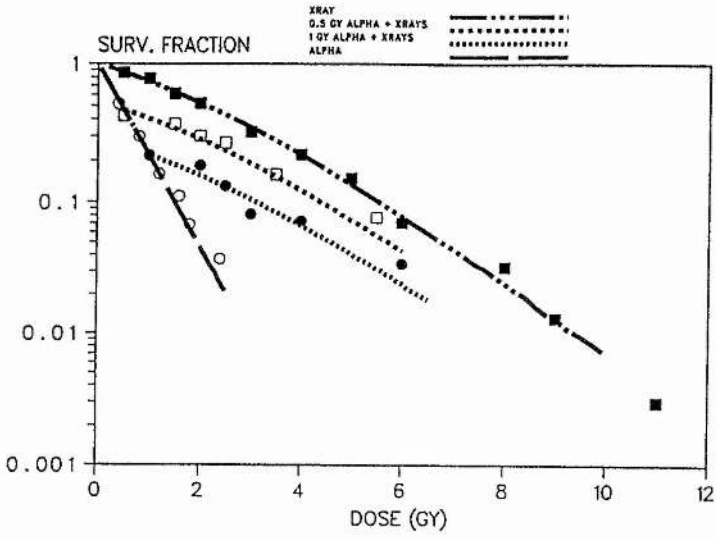
iii. Ngo et-al 1981 for asynchronous Chinese Hamster V79 cells [88].

The results are plotted (refer to figure 2.1) against the experimental data and are satisfactory.

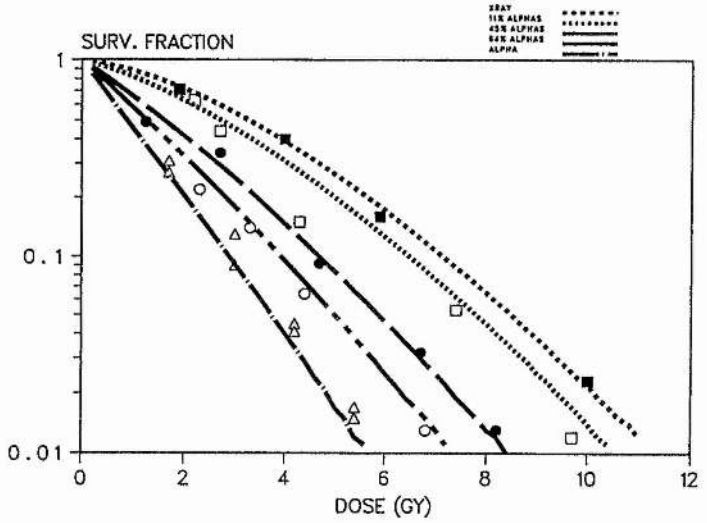
Table 2.1: The parameters used in testing LPL (Curtis) Model.

Parameters	Barendsen	Raju and Jett		Ngo et-al
		Aerobic	Hypoxic	
Particles	α	α	α	neon ions
LET (keV/μm)	170	210	210	183
z^{*2}/β^2	3052	3980	3980	1549
σ_o (μm^2)	45	27	27	45
F_{PL}	0.1	0.1	0.1	0.1
n	12	12	12	12
k_o	2.5E-04	2.5E-04	1.7E-04	2.5E-04
X-rays radiation				
$\eta_L(Gy^{-1})$	0.2531	0.0767	0.0402	0.1313
$\eta_{PL}(Gy^{-1})$	0.8792	1.0	0.4177	0.7711
ε	10	10	10	10

Panel a



Panel b



Panel c

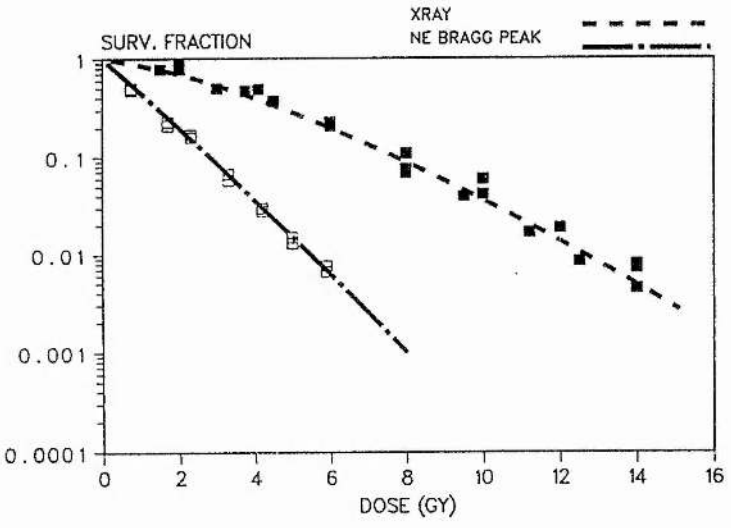


Fig. 2.1: Comparison of experimental cell survival data with theoretical predictions of LPL model by Curtis. Panel a; is using Barendsen et-al data, panel b; is using Raju and Jett data, and panel c; is using Ngo et-al data.

2.4.2. Pairwise Lesion Interaction (PLI) Model (Harder)

2.4.2.1. Introduction

The Pairwise Lesion Interaction Model (PLI) by Harder [89] is based on the concept originated from Lea's model [62], namely that lesions can interact pairwise (i.e. interaction can occur between two lesions). Interaction between primary lesions (i.e. molecular lesions not yet fully repaired and temporarily able to interact pairwise) formed by radiation, is assumed to occur in contact regions, namely the regions with contact between different chromatin fibres or between sections of the same fibres. Among the endpoints considered under the PLI model are exchange-type chromosomes aberration and reproductive cell death (cellular survival). The dose-mean restricted linear energy transfer with cut-off energy Δ=100 eV ($L_{100,D}$) is used as the fundamental track structure parameter of the charged particle. According to Harder [90], it has been possible to demonstrate a linear dependence of yield coefficient α (per Gy) upon $L_{100,D}$ for the production of dicentric chromosome aberrations in human lymphocytes, for survival from reproductive death of V 79 cells, and other cytological end-points as well.

2.4.2.2. Basic principles

In the nuclear chromatin, it is assumed that there are some regions with contact between different chromatin fibres or between sections of the same fibre, which are in temporary existence, due to its conformation changes and thermal movement (refer to figure 2.2). Radiation-induced primary lesions such as molecular lesions which have not yet been fully repaired, are formed in the contact (interaction) regions as well as in other part of the nuclear chromatin. In this model, the primary lesions in the contact region, are assumed to be able to interact pairwise.

Suppose that there are n reactive lesions in a contact region, there will be $a.\binom{n}{2}$

pairwise contacts per unit time, where a is the proportionality factor [91]. The probability per unit time of pairwise interaction in a contact point is given by

$a.k.\binom{n}{2}$, where k is the interaction efficiency. For an irradiated cell nucleus,

the mean interaction rate at time t is given by: $\epsilon(t) = ak\overline{\binom{n}{2}}$, where

$\overline{\binom{n}{2}} = \frac{1}{2}(\overline{n^2} - \overline{n})$.

Suppose that the passage of an ionizing particle contributes to the region a stochastic number of lesions, of which n_1 are reactive at time t. For passage of υ particles, the cumulants are $\overline{n} = \nu\overline{n_1}$, and $\overline{n^2} - \overline{n}^2 = \nu(\overline{n_1^2} - \overline{n_1}^2)$.

So that $\overline{n^2} - \overline{n} = \nu(\overline{n_1^2} - \overline{n_1}^2 - \overline{n_1}) + \nu^2\overline{n_1}^2$.

If υ follows a Poisson distribution with $\overline{\ } = $, $\overline{\ } = \ +1$, then averaging over υ and substituting into $\varepsilon(t)$, the mean interaction rate at time t for each contact region in a cell nucleus is given by: $\epsilon(t) = \frac{ak}{2}[m(\overline{n_1^2} - \overline{n_1}) + m^2\overline{n_1}^2]$.

However m is proportional to absorbed dose D. So $\varepsilon(t)$ exhibits a linear quadratic dose dependence. The first term is due to intra-track and the second term, due to inter-track interactions. Harder derived mathematically the expression for $\varepsilon(t)$ and obtained the following result: $\epsilon(t) = \frac{akp^2(t-\tau)}{2}[(\frac{\overline{i^2}}{\overline{i}} - 1)cD + c^2D^2]$

where $p(t-\tau)$ is the probability for an ionization, produced at time τ, to result in a primary lesion at time t;

m is proportional to absorbed dose D;

i is the number of ionizations per particle traversal; and

$\frac{\overline{i^2}}{\overline{i}} - 1$ is the microdosimetric factor.

The result shows the linear-quadratic dose dependence regularly observed in chromosome aberration induction experiments.

The contact region has nanometre dimensions in Harder model and can be simulated in microdosimetry. The linear term in $\varepsilon(t)$ is proportional to the microdosimetric factor $\frac{\overline{i^2}}{\bar{i}} - 1$. Harder et-al [91] have studied the properties of this factor for interaction regions of nanometre dimensions, for which a linear dependence of $\frac{\overline{i^2}}{\bar{i}} - 1$ on $L_{100,D}$ has been established as shown in figure 2.3. The experimental result on the $L_{100,D}$ dependence of yield coefficient α (Gy^{-1}) for dicentric chromosomes in human lymphocytes, as shown in figure 2.4, has strongly supported the expression for $\varepsilon(t)$, which is mathematically derived.

The complete expression for $\varepsilon(t)$ obtained by Harder is given as follows:

$$\epsilon(t) = \frac{a.k}{2}\left[\left(\frac{\overline{i^2}}{\bar{i}} - 1\right)\int_o^t p^2(t-\tau)\, c\dot{D}(\tau)\, d\tau + \left(\int_o^t p(t-\tau)\, c\dot{D}(\tau)\, d\tau\right)^2\right]$$

where c is the factor for region size;

p is the factor for repair kinetics; and

$\dot{D}$ is the dose rate in time $d\tau$.

In the PLI model, the important number is the average production rate of pairwise lesion interaction products per cell, r(t), which is the product of $\varepsilon(t)$ and the number N of the interaction regions, i.e. $r(t)=N.\ \varepsilon(t)$. The pairwise lesion interaction is in competition with lesion repair. The amount of intra-track interaction (i.e. proportional to dose) between radiation-induced primary lesions in chromatin, will depend on the balance between interaction distance and particle track structure (LET effect). The amount of inter-track interaction (i.e. proportional to dose squared) reflects the balance between the lifetime of repairable lesions and their production rate (i.e. effects of fractionation and protraction).

2.4.2.3. Survival equation

The survival fraction (SF) according to this model is given by:

$$SF=\exp\left[-(Ln\ n)\left(\exp\left(-\frac{D}{D_q}\right)+\frac{D}{D_q}-1\right)\right]$$

where

n is the extrapolation number; and

D_q is the shoulder dose.

2.4.2.4. Model Appraisal

$L_{100,D}$ is used as the physical parameter for radiation in this model. The PLI model by Harder utilizes 'pairwise of lesion interaction' as a basis to derive the model. The model takes care of the following:

i. Intra-track interaction (i.e. proportional to dose) in the contact regions in nanometre region [92];

ii. Inter-track interaction which is proportional to dose squared in the nanometre region;

iii. Repair process which competes with the lesion interaction [93]; and

iv. The δ-rays exceeding 100 eV by taking $L_{100,D}$ as the fundamental track structure parameter.

However from the equation for the survival curve (SF) for the model, given by:

$$SF=\exp\left[-(Ln\ n)\left(\exp\left(-\frac{D}{D_q}\right)+\frac{D}{D_q}-1\right)\right]\ ;$$

i. It is common that not all survival curves possess extrapolation number n; and

ii. Not all survival curves have D_q especially for high LET radiation.

2.4.2.5. Testing Harder's model

Harder has used data for the production of dicentric chromosome aberrations in human lymphocytes, and data from the reproductive death of V 79 cells, to test his model [94].

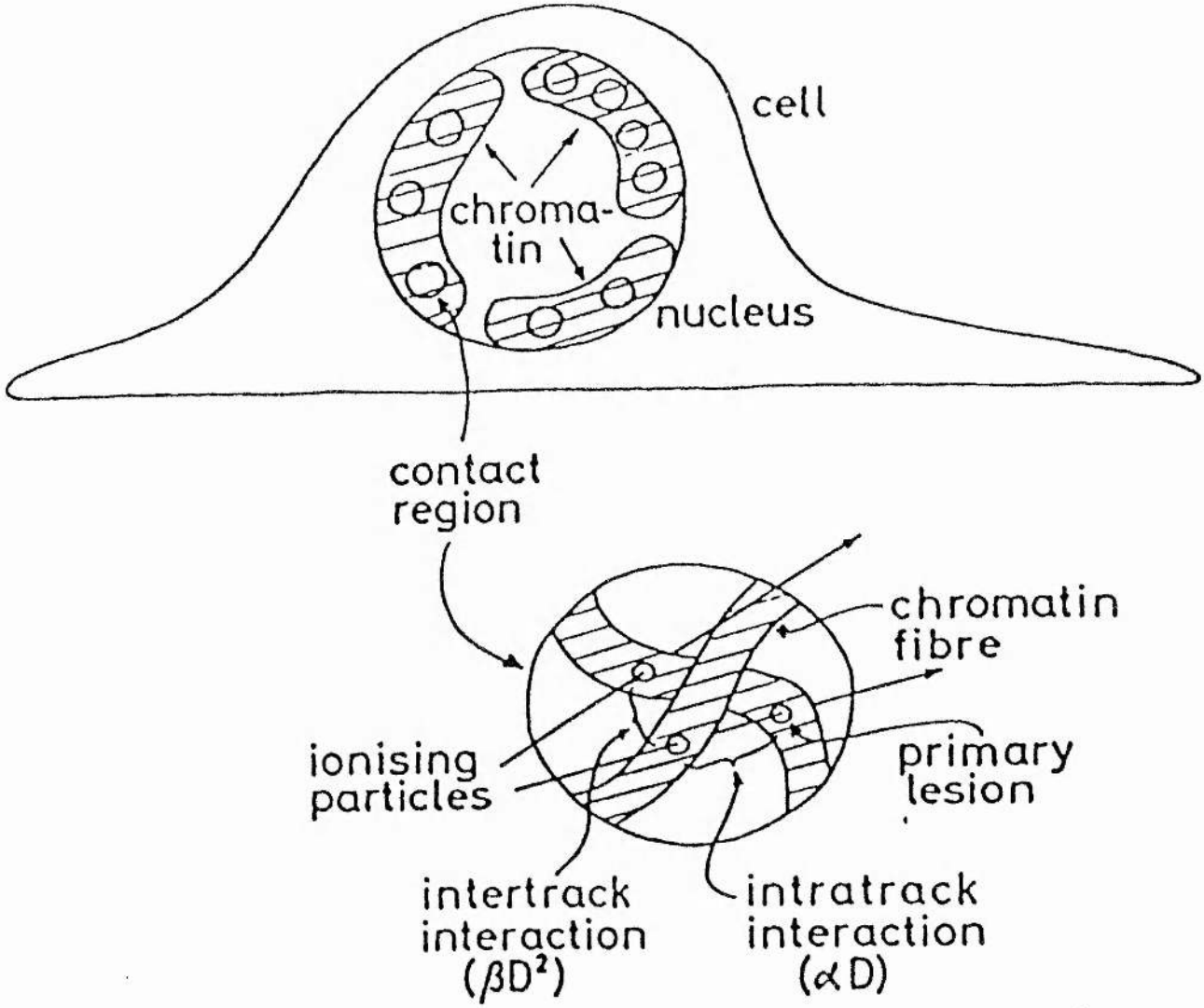


Fig. 2.2: Pairwise Lesion Interaction in Chromatin (scheme)

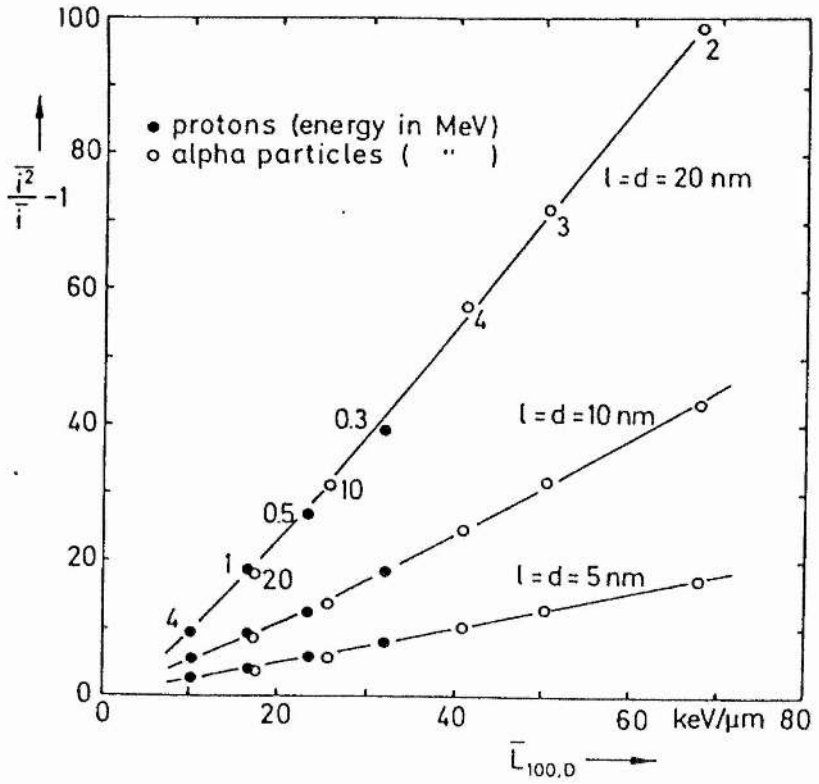


Fig. 2.3: Restricted LET ($L_{100,D}$) dependence of quantity $\left(\frac{\overline{i_1^2}}{\bar{i}_1} - 1\right)$ for cylindrical targets hit by protons and alpha particles, calculated by Harder et-al 1987 from energy deposition distributions obtained by Charlton 1985.

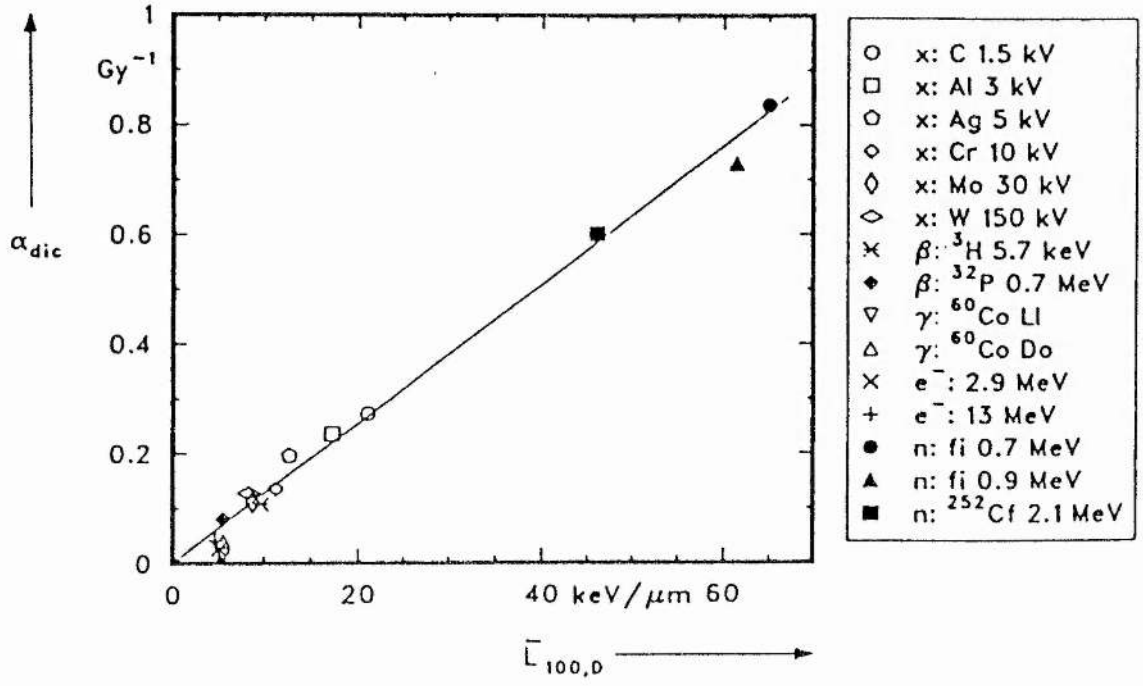


Fig. 2.4: Restricted LET dependence of yield coefficient α for dicentric chromosomes in human lymphocytes.

2.4.3. Cellular Track Structure (CTS) Model (Katz)

2.4.3.1. Introduction

The model by Katz [95] for cellular survival after heavy ion irradiation, is based on his track structure model developed earlier for various ionizing radiation detectors which include observable tracks in nuclear emulsion, dry enzyme and viruses, scintillation counters, TLD and Fricke dosimeter. Katz claims the model is applicable to gamma and heavy ion irradiations. Inactivation of cells by a beam of particles is assumed to proceed independently by two modes of damage namely ion-kill mode with exponential survival characteristic, and gamma-kill mode (multi-target, single hit) with sigmoid survival characteristic. Four parameters are required in the model to represent biological cells, under a specific ambient condition: a critical dose E_o, the target multiplicity m to describe their response to γ rays, and two additional parameters κ and σ_o to describe their response to heavy ions. The model is sometimes called a Two Component Model due to the fact that radiation can be considered to consist of low (gamma kill) and high LET (ion kill) components.

2.4.3.2. Basic Principle

In principle Katz deduces the mean number of hits due to δ-rays, per target located in a thin cylindrical shell with thickness dt at distance t from the ion path. The δ-rays are assumed to be emitted at right angles to the ion path and to have a simple range energy relationship given by t=KT, where t is the range and T is its kinetic energy. The fraction of targets inactivated in the thin shell is determined by using the Poisson probability laws of conventional target theory. In the cellular track model by Katz, z^2/β^2 is used as an important quality parameter which is proportional to the yield of delta rays per unit distance along a fast ion track. The model distinguishes between the track width regime and the grain count regime [96][97]. The grain count regime is where the inactivation occurs randomly along the particle's path, like 'beads on a string'. The cells within the gap i.e. between the activated cells, may be damaged sub-lethally because of fluctuations in the production of δ-rays. Cells which are not killed in the ion-kill mode by the passage of a single ion, may be damaged further and killed by δ-rays from the adjacent ion at high fluence i.e. inter-track effect. δ-rays are only able to inactivate

a fraction (P), of the cells intersected by the ion. The range and number of δ-rays are limited and cannot activate remote targets giving the appearance of 'hairy rope' as in the track width regime. The result in the grain count regime is that the track has the appearance of a random string of beads. P is the fraction of cells that are killed (inactivated) by ion-kill. P also represents the fraction of energy deposited by the ion that contributes to killing in the ion-kill mode. (1-P) represents the fraction of cells that are killed in the gamma-kill mode and also represents the fraction of energy deposited in the gamma-kill mode.

The track width regime is where the inactivations are distributed like a 'hairy rope'. For high Z (nuclear charge), δ-rays that are produced, have sufficient number and range to activate remote target giving the appearance of 'a hairy rope'. In the track width regime P is greater than 0.95 and as σ/σ_0 increases, the dose deposited in gamma-kill mode is approximated as zero. The transition from the grain count to the track width regime takes place in a plateau, in the neighbourhood of $z^{*2}/\kappa\beta^2$ of about 4, which corresponds to $\sigma=1.4\pi a_0^2$. κ(or a_0) represents the size of internal cellular targets. At lower values is the grain count regime, and at higher values is the track width regime. After the plateau, the cross-section rises in the track width regime then falls down in the thindown region. Thindown is due to a kinematic limit on the energy and hence the range of δ-rays produced, which occur at the end of the track. The effective charge z^* is given by: $z^*=Z[1\text{-}\exp\text{-}125\beta Z^{-2/3}]$

There are two modes of inactivation in the cell survival model by Katz, namely ion kill mode and gamma kill mode. 'Ion-kill' is defined as a response produced by the passage of a single ion through or adjacent to a target. It fully describes a low fluence irradiation where it is unlikely that δ-rays from different ions in a beam will intersect in a single cell. 'Gamma-kill' is defined as a response to δ-rays from different ions, overlap i.e. inter-track effect, which can be described by the same equation used for cell survival (SF) after γ-irradiation given by formula $SF=1-(1-\exp(-h))^m$ where m is the target number and h is the mean number of hits in each target. The radiation effect is based on the dose deposited (by δ-rays) in, rather than the number of electron (or δ-rays) passing through, the nucleus (i.e. the sensitive site). Cells inactivated by the passage of a single heavy ion are said to be inactivated

in ion-kill mode in the grain count regime with the inactivation cross section (σ) less than the saturation inactivation cross section (σ_o). In the track width regime the inactivation cross-section (σ) may be greater than σ_o.

2.4.3.3. Ion-kill Inactivation Cross-section σ

Katz calculates the ion-kill inactivation cross-section σ, by integrating the probability P, for inactivation which is given by the expression suitable to multi-target single hit statistics, over all space about the ion's path. P is given by the following formula:

$$P=[1-\exp[-\frac{\bar{E}(z,\beta,t,a_o)}{E_o}]]^m$$

where

$\bar{E}$ is the mean dose due to δ-rays in a sensitive element of radius a_o;

E_o is the critical dose after γ-ray irradiation;

m is the target number;

t is the distance between the sensitive element centre and the ion's path; and

a_o is the radius of the sensitive element.

The ion-kill inactivation cross-section σ, is given by:

$$\sigma=\int_o^{\tau} 2\pi t[1-\exp(-\frac{\bar{E}}{E_o})]^m dt$$

where τ is the maximum range of the δ-rays.

The numerical integration of σ, for different values of E_o, a_o, z, β, m and κ, is shown in figure 2.5.

2.4.3.4. Survival Fraction SF

The total survival fraction (SF) of the irradiated cells is given by multiplying the ion-kill mode survival probability (Π_i) with the gamma-kill mode survival probability (Π_γ) (i.e.$SF=\Pi_i.\Pi_\gamma$). The survivors of the ion-kill mode of damage is the initial population for the gamma-kill mode.

When a thin specimen of the medium is irradiated with a beam of particles of fluence ϕ, and LET L, a dose $D=\phi L$ will be deposited of which an amount PD is deposited in the ion-kill mode and an amount (1-P)D is deposited in the gamma kill mode. The inactivation of cells by a beam of particles is assumed to proceed independently by these two modes, namely ion-kill mode with exponential survival characteristic and gamma-kill mode with sigmoid survival characteristic. The radiosensitivity parameters for CTS model are m, E_o, σ_o and κ.

There are two possible regimes where the cell inactivation will take place namely the grain count regime and the track width regime. From the value of $z^{*2}/\kappa\beta^2$, it is possible to determine whether a particular track segment irradiation is in the grain count regime or in the track width regime.

2.4.3.4.1. SF in the Grain Count Regime

The cell survival fraction (SF) in this regime is given by:

$$SF = \Pi_i.\Pi_\gamma$$

The ion-kill survival probability is given by:

$$\Pi_i = \exp(-\sigma\phi); \text{ or}$$

$$\Pi_i = \exp(-\sigma D/L).$$

where σ can be derived from: $\sigma/\sigma_o=P=[1-\exp-(z^{*2}/\kappa\beta^2)]^m$.

The gamma-kill mode survival probability is by:

$$\Pi_\gamma = 1-[1-\exp-(1-P)D/E_o]^m$$

The survival fraction in the grain count regime is given by:

$$SF= \exp(-\sigma\phi)\{1-[1-\exp-(1-P)D/E_o]^m\}$$

2.4.3.4.2. SF in the Track Width Regime

The survival fraction (SF) is given by:

$$SF=\Pi_i.\Pi_\gamma$$

The value of P is bigger than 0.95 i.e. $P>0.95$ and the value for the gamma-kill mode survival probability is approximated to be equal to one i.e. $\Pi_\gamma=1$.

The ion-kill mode survival probability is given by:

$$\Pi_i = \exp(-\sigma\phi)$$

σ can be deduced from the figure 2.5: σ/a_0^2 against $z^{*2}/\kappa\beta^2$, in the track width regime.

The survival fraction in the track width regime is given by:

$$SF = \exp(-\sigma\phi).$$

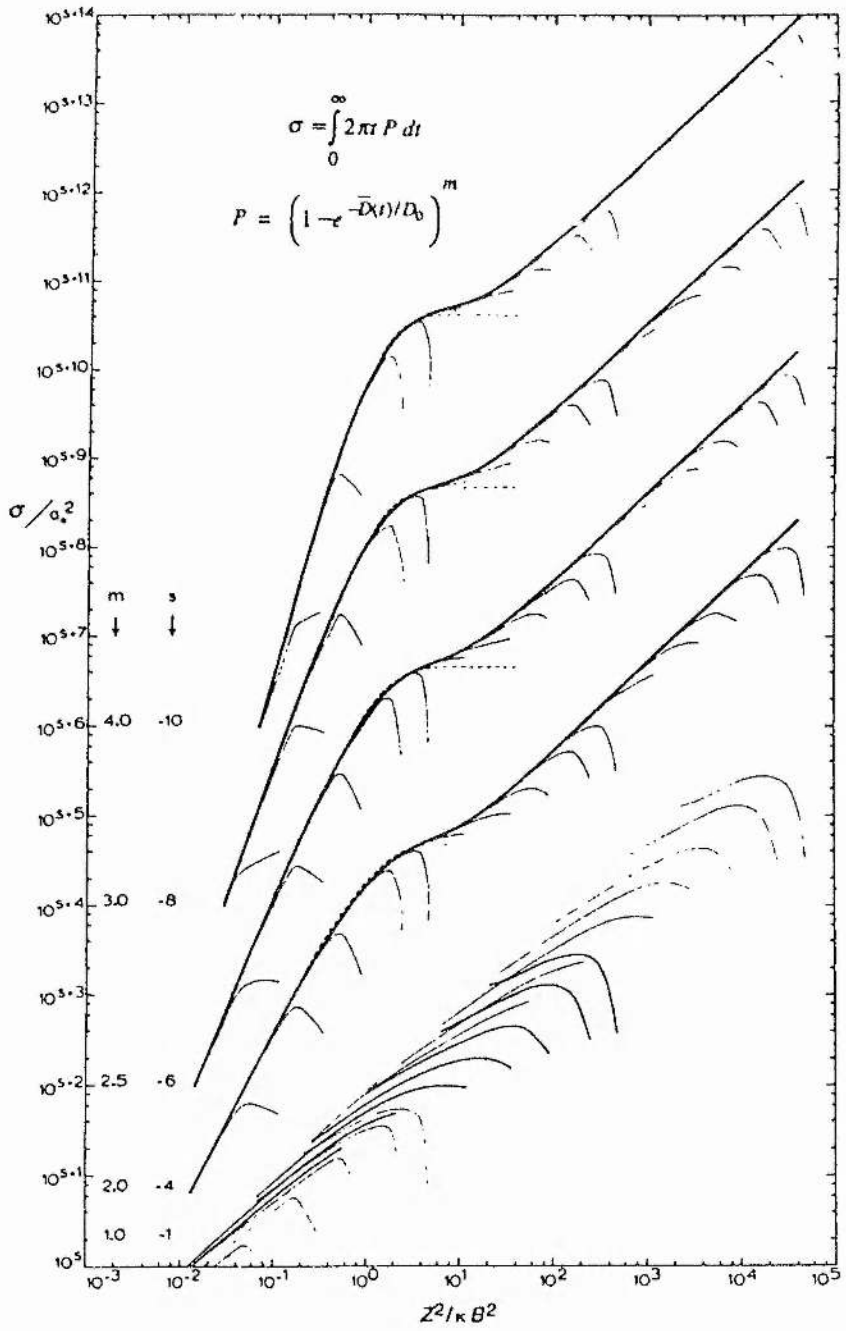


Fig. 2.5: The numerical integration of σ for different values of E_o, a_o, z,β, m and κ, versus $z^2/\kappa\beta^2$.

Table 2.2: Characteristics of the grain count and track width regimes, for multi-target single hit calculation

In the grain count regime	In the track width regime
i. The slope of the envelope is equal to m, the target number.	i. The slope of the envelope is equal to one (i.e. m=1)
ii. At low $z^{*2}/\kappa\beta^2$ the following approximation for σ/σ_0 is valid; $\sigma/\sigma_0=[1-\exp-(z^{*2}/\kappa\beta^2)]^m$.	ii. The value for σ/σ_0 is greater than one.
iii. The plateau exists at the upper end of $z^{*2}/\kappa\ \beta^2$ at values of; (a) $z^{*2}/\kappa\ \beta^2=4$; and (b) $\sigma=\sigma_0$;the saturation ion-kill inactivation cross-section. The width and flatness of the plateau increases with increasing m.	iii. The plateau exists at the lower end of $z^{*2}/\kappa\ \beta^2$ at values of (a) $z^{*2}/\kappa\ \beta^2=4$; and (b) $\sigma=\sigma_0$ the saturation ion-kill inactivation cross-section, and occurring at such a value of z^{*2}/β^2 that every sensitive element through which the ion passes is sensitized.
iv. In the grain count regime the fraction of dose P, deposited in the ion kill mode is less than one. i.e. $P=\sigma/\sigma_0<1$	iv. In the track width regime the fraction of dose P, deposited in the ion-kill mode is one i.e. $\sigma/\sigma_0>1$ and P=1
v. There is no thindown phenomena in the grain count regime.	v. Thindown phenomena exists due to the decreasing radial distance τ to which the δ-rays penetrate.
vi. Gamma-kill mode can occur only in the grain count regime. The damage mechanism can be ion-kill mode and gamma kill mode. The fraction of intersected cells inactivated by a single passing ion (i.e. ion-kill) in the grain count regime is given by P, which is equal to $\sigma/\sigma_0=[1-\exp-(z^{*2}/\kappa\beta^2)]^m$.	vi. The damage mechanism is one hundred percent ion-kill mode. The value of Π_γ is equal to one. (i.e. $\Pi_\gamma=(1-(1-\exp(-E/E_0))^m)$). σ initially rises and finally decreases rapidly due to the 'thindown' [98].

In the grain count regime	In the track width regime
vii. The cross-section in the grain count regime is given by; $\sigma/\sigma_o=[1-\exp-(z^{*2}/\kappa\beta^2)]^m$.	vii. The cross-section in the track width regime is derived as follows; a. find 'target cross-section' for a target of radius a_o from the equation: $\kappa=E_o a_o^2 \times 5\times10^6$ E_o and m must be found from the cell survival response after γ-rays irradiation: and b. by using the standard figure i.e. figure 2.6: σ/a_o^2 versus $z^{*2}/\kappa\beta^2$, assume that $\sigma/\sigma_o=1$ at $z^{*2}/\kappa\beta^2=4$. Find the value of $z^{*2}/\kappa\beta^2$ from the experimental set-up, then find σ from the graph. Note: κ (or a_o) represents the size of internal cellular target.
viii. This is unsaturated region.	viii.This is saturation region (i.e. P >0.95)

2.4.3.5. Model Appraisal

According to Katz [13] the model is purely physical (i.e. statistical and parametric rather than mechanistic) and rests on its fit to data rather than on its relationship to a presumed mechanism. A eucaryotic cell is assumed as a bean bag: the bag represents the cell nucleus and the beans represent the internal targets.

The model:

i. is able to fit many experimental data such as by Young, Underbrink and Skarsgard (see section 2.4.3.6) through four radiosensitive parameters (m, E_o, κ and σ_o) [99];

ii. is applicable to nuclear emulsions, enzymes, viruses, bacteria, scintillation counters and eucaryotic cells;

iii. take cares of the cumulative effect (gamma kill mode, the sigmoid survival characteristic) due to the low LET component, as well as non-cumulative effect (ion-kill mode, the exponential survival characteristic) due to the high LET component;

iv. appropriately, has used cross-sections to indicate the interaction probability in both the grain count regime and the track with regime and has successfully explained the increasing cross-section with increasing z^2/β^2, and the thindown phenomena;

However the model:

i. is not applicable to electron irradiation; and to neutron data as discussed by Waligorski [100] because z^2/β^2 is invalid for low energy protons;

ii. basically uses dose (i.e. due to δ-rays) to quantify the radiation, which is argued against by a few authors including Katz himself;

iii. does not take care of:

   a. repair phenomena of the damage, lesion or sub-lesion;

   b. effects of cell cycle which can alter the sensitivity of the cells toward radiation;

   c. effect of dose rate, dose fractionation or protraction;

   d. inverse dose rate effect, and internal emitters etc.

Furthermore the splitting of dose into gamma kill mode and ion kill mode is artificial. The parameter z^2/β^2 used as a physical parameter of radiation in the model

has a two-fold physical interpretation. z^2/β^2 can be interpreted either as the yield of δ-rays per unit track or as the primary ionisation along the track (the inverse of the mean free path λ). The model does not explicitly identify the energy requirement to inactivate a biological target. The model assumes that the effect produced by secondary electrons from γ-rays and secondary electrons from heavy ions at the same dose, are comparable, which is a very crude approximation as the effect can vary considerably. For example the D_o's for carbon K_α X-rays and ^{60}Co γ-rays differ by a factor of two [10].

2.4.3.6. Testing Katz's model

Katz has used very extensive sets of data obtained by other researchers to test his model. This includes data by:

i. Skarsgard et-al [101] $CH2B_2$ Chinese Hamster Cells irradiation;

ii. ˆYang et-al [102] C3H1OT1/2 Mouse Cells irradiation; and

iii. Underbrink et-al [103] Tradescantia irradiation.

The values of m, κ,E_o and σ_o extracted from data used in the test are listed in table 2.3. According to Katz's model the survival fraction is given by the following equations:

$$F=\exp\left(-\frac{\sigma D}{L}\right).\left[1-\left[1-\exp-\left[(1-P_L)\frac{D}{D_{\gamma,o}}\right]\right]^m\right]$$

$$lnF=-\frac{\sigma D}{L}+\ln\left[1-\left[1-\exp-\left[(1-P_L)\frac{D}{D_{\gamma,o}}\right]\right]^m\right]$$

Using D=ϕ.L and assuming that:

$$A=\left[1-\left[1-\exp-\left[(1-P_L)\frac{D}{D_{\gamma,o}}\right]\right]^m\right]$$

So $lnF=-\sigma\Phi+\ln A$

$$\frac{d(lnF)}{d\Phi}=-\sigma+\frac{dlnA}{d\Phi}=-\sigma+\frac{\frac{dA}{d\Phi}}{A}$$

$$\frac{dA}{dQ} = \frac{dA}{dD} \cdot \frac{dD}{d\Phi}$$

$$\frac{dA}{dD} = -m[1-\exp-(1-P_L)\frac{D}{D_{\gamma,o}}]^{M-1} \cdot [(-1)(-\frac{(1-P_L)}{D_{\gamma,o}}\exp-[(1-P_L$$

or: $$\frac{dA}{dD} = -m\frac{(1-P_L)}{D_{\gamma,o}}\exp-(1-P_L)\frac{D}{D_{\gamma,o}} \cdot [1-\exp-(1-P_L)\frac{D}{D_{\gamma,o}}]^{M-1} \cdot$$

Then: $$\frac{dD}{d\Phi} = \frac{1}{L}$$

The final expression for the effective cross section is given as follows:

$$\frac{d\ln F}{d\Phi} = -\sigma - \frac{1}{L} \cdot \frac{[m\frac{(1-P_L)}{D_{\gamma,o}}\exp-(1-P_L)\frac{D}{D_{\gamma,o}}[1-\exp-(1-P_L)\frac{D}{D_{\gamma,}}}{[1-[1-\exp-(1-P_L)\frac{D}{D_{\gamma,o}}]^m}$$

Table 2.3: Values of m,κ,E_o and σ_o extracted from survival data used by Katz.

Authors	Cell types	m	κ	E_o (erg cm^{-3}	σ_o (cm^2)	Notes
Skarsgard et-al	$CH2B_2$ Chinese Hamster Cells	3	1100	1.82	$4.3x10^{-7}$	
Yang et-al	C3H1 OT1/2 Mouse cells	3	750	1.7	$5x10^{-7}$	
Underbrink et-al	Tradescantia	2 or 1.5	1000 1900	2.1 2.6	$3.5x10^{-7}$ $4.0x10^{-7}$	

2.4.4. Hit Size Effectiveness (HSE) Model (Bond and Varma)

2.4.4.1. Introduction

In this model, the hit size effectiveness function (HSEF) is deduced to indicate the induction probability of all-or-none effect with respect to the magnitude of energy imparted in a single event i.e. lineal energy [104]. This is an application of microdosimetry in the biophysical modelling of radiation action. The theory of microdosimetry requires detailed knowledge of the energy deposition in sensitive sites as a pre-requisite to estimate survival curves. When a population of cells is irradiated with ionizing radiation, various magnitudes of energy will be imparted in the critical volume of each cell [105]. Subsequently the hit effectiveness ratio (ε), namely the fraction of hits which result in the all-or-none effect, and the incidence (I), of the all-or-none effect will be deduced [106]. From this the survival fraction of a specified biological end-point can be determined. The term quantal cell response or all-or-none effect [106], denotes responses which are not usually reversible spontaneously. e.g. Chromosome abnormalities, mutations, neoplastic cell transformations or cell death. Such responses are scored either by noting their presence in the individual cell, or by scoring abnormalities presumably derived from a single quantally altered cell.

2.4.4.2. Basic Principle

When a population of cells is placed or exposed in a charged particle field (i.e. due to indirectly or directly ionising radiations) of dose D, no matter how small, there is a chance of a stochastic encounter involving the charged particle(s) and the cell(s) [107]. Such stochastic encounters result in a wide spectrum of:

i. possible sizes of (single) hits (i.e.magnitude of energy imparted) on;

ii. possible sizes of microdosimetric events (i.e. different magnitude of events for each track) in; or

iii. possible sizes of cell doses to;

the critical volume of the cells or the critical effective target volume.

Absorbed dose expresses the average energy deposited per unit mass of the irradiated medium. At extremely low doses, absorbed dose loses its significance as a good indicator of biological damage, due to its fluctuation. At lower doses the

spatial energy deposition becomes important, and for this reason Bond and Varma [75] apply microdosimetry in developing this model.

To expose a population of cells means one or more charged particles, moving in the vicinity of the cells, quantifiable in terms of fluence Φ. Stochastic transfer of energy to a critical volume of cross section σ, can cause injury to the cell, the severity of which depends on the event size. Usually quantal cell response denotes irreversible changes . All sub-effective cell injuries such as single strand breaks, are not considered as quantal cell response because they are not observable in individual cells and are usually repairable. High level radiation (HLR) is a strong field in which each cell is hit at least once. Any further increase of Φ, can result only in additional (multiple) hits per cell. In low level radiation (LLR), only a small fraction of the exposed cells are hit, so the frequency of multiple hits on the same cell is negligibly small (effectively all hit cells are singly hit). HLR and LLR refer to low and high probability of interaction, and not necessarily to large or small energy deposits in the cell critical volume. The hit size on a cell is defined as the amount of energy transferred to and deposited in the cell critical volume.

$$\varepsilon = \varepsilon_{in} - \varepsilon_{out}.$$

The energy transfer causes injury to that cell critical volume, the severity of which depends on magnitude of the transfer. Above some minimal level of severity (threshold), the cell will show a quantal response.

The incidence of hit cell I_H, is given by :

$$I_H = \Phi\sigma;$$

or $$I_H = \phi t_e \sigma$$

where

σ is the average cross section of the cell critical volume;

Φ is the integral fluence;

ϕ is the fluence rate; and

t_e is the exposure time.

The total I_H is proportional to, or has a linear (no threshold) relationship with Φ. I_H is also an expression of risk of a hit on an individual cell in the exposed population. However it provides only the average value for all cells in the exposed population, from which the true risk for any given cell can not be determined. The cell critical

volume is a non-anatomical volume within the cell, the apparent mean diameter or 'cross-section' σ of which can be calculated, and within which the macromolecular target(s) must reside. The tissue content of critical volume must be hit in order for the chance of a quantal response to be other than zero.

The actual total incidence of hit cells cannot be determined in living cells. However this incidence of hit cells, I_H, can be indirectly estimated by using a microdosimetric proportional counter (mpc). The mpc is viewed as a phantom of cell critical volume which is filled with tissue equivalent gas and at reduced pressure, so that the number of interactions per charged particle is the same as that for the cell critical volume. A very large number of single events and their size can be recorded in a relatively short time in a low strength field because of the large diameter of the chamber, relative to the that of the cell critical volume. When adjusted or 'scaled' to the dimension of a cell critical volume and to the LLR field of interest, which may involve a factor well in excess of 10^6, the converted reading does provide the small number of hit cells per cell. The mpc can record very large numbers of single events and their sizes. If I_H is known, Φ can be found by; $\Phi = I_H/\sigma$.

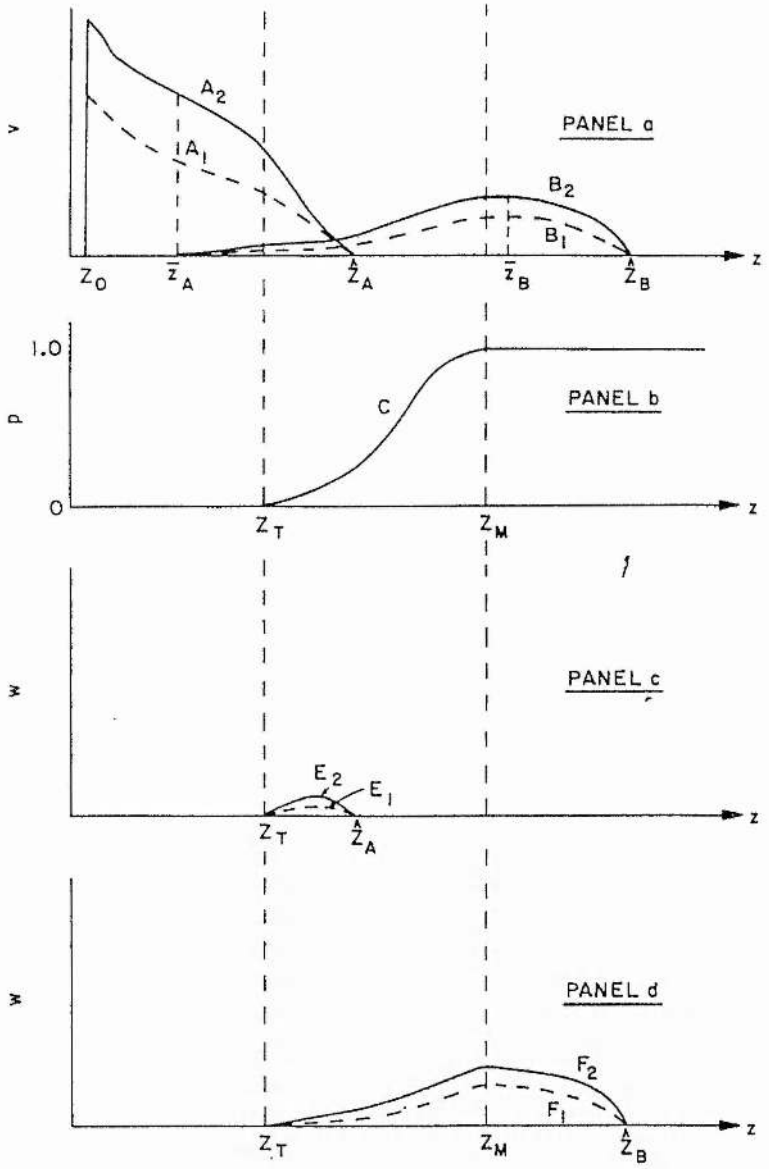


Fig. 2.6: Schematic functions to illustrate the calculation of the expected incidence of the single cell, stochastic effect. In panel a is shown v, the hit incidence density (or the number of cell doses for unit cell dose size), versus z, the cell dose size (or the specific energy). The different letters (A and B) refer to spectra for two different radiation qualities. The subscripts 1 and 2 for each radiation quality refer to doses D_1 and D_2 shown also in figure 2.7. Z_o corresponds to the ionization threshold. $\bar{z}_A$ and $\bar{z}_B$ are mean z values, $\hat{Z}_A$ and $\hat{Z}_B$ refer to maximum z values, for the corresponding spectra, and Z_M is the value of z above which the hit probability is effectively 1.0. In panel b is shown p, the probability of an all-or-none single cell effect per dosed cell , versus the cell dose z. In panel c is shown w, the expected all-or-none single cell effect incidence density (or the incidence per unit cell dose of size z), as a function of z, for the low LET radiation A. The subscripts for distributions E_1 and E_2 correspond to the same subscripts for spectra A and B in panel a. In panel d is shown the same plot as in panel c, but for the high LET radiation B (reference [108]).

In figure 2.6. D_1 and D_2 are absorbed doses of low and high LET radiation. The horizontal axes for all four panels in figure 2.6. are the specific energy for single hits (or events) to the critical volume. The vertical axes for all four panels are:

i. v. the hit incidence density $d\mu_H/dz$;

ii. p the probability of the all-or-none effect;

iii. for panel c and d. w is the effect incidence density $d\mu_K/dz$. under the assumption that when D_1 and D_2 are sufficiently small, equal to dI_E/dz.

Panel a: A_1 is the microdosimetric, specific energy spectrum for quality A of dose D_1. A_2, B_1 and B_2 are the microdosimetric, specific energy spectra for quality A of dose D_2, quality B of dose D_1 and quality B of dose D_2, respectively.

If g_H is the hit incidence density function, so:

$v=g_{H.A}(z:D_1)$ for A_1; the hit incidence (i.e.area under the curve) corresponds to $\mu_{H.A}(D_1)$;

$v=g_{H.A}(z:D_2)$ for A_2; the hit incidence $\mu_{H.A}(D_2)$;

$v=g_{H.B}(z:D_1)$ for B_1; the hit incidence $\mu_{H.B}(D_1)$; and

$v=g_{H.B}(z:D_2)$ for B_2; the hit incidence $\mu_{H.B}(D_2)$.

If the corresponding normalised microdosimetric spectra i.e. the probability density functions (or probability distributions) from the two qualities are $f_A(z)$ and $f_B(z)$. then the hit incidence density functions are given as follows:

$g_{H.A}(z:D_1) = \mu_{H.A}(D_1).f_A(z)$;

$g_{H.A}(z:D_2) = \mu_{H.A}(D_2).f_A(z)$;

$g_{H.B}(z:D_1) = \mu_{H.B}(D_1).f_B(z)$; and

$g_{H.A}(z:D_2) = \mu_{H.B}(D_2).f_B(z)$.

The mean hit sizes are given by:

$$\overline{z}_A = \int_{z_o}^{\hat{z}_A} z f_A(z)\, dz$$

and $\bar{z}_B = \int_{z_T}^{z_M} z f_B(z)\, dz$

D is the specific energy averaged over the entire population of critical volumes both hit and unhit, whereas the values of $\bar{z}_A$ and $\bar{z}_B$ apply only to critical volumes which are hit.

$D = \mu_{H.A}(D).\bar{z}_A$;and

$D = \mu_{H.B}(D).\bar{z}_B$.

If dose D for radiation quality A is the same for radiation quality B, for any value of D:

$\mu_{H.A}(D)/\ \mu_{H.B}(D) = \bar{z}_B/\ \bar{z}_A$

i.e. the ratio of hit incidence for the two qualities with the same dose for any value of dose (D), and is in the single-hit range for both, is equal to the inverse of mean hit size.

Panel b: The cell dose-cell response function $P=\pi(z)$.

P is the probability that a cell with a given hit size z, will manifest the all-or-none effect. Its value is zero (p=0) for $z \leq Z_T$ and rises from 0 to 1 in the range of Z_T to Z_M and p=1 for $z \geq Z_M$.

Panel c: The curves E_1 and E_2 are plots of the effect incidence density functions for quality A; which are the products of the functions represented by curve A_1 and A_2 in panel a; and the cell dose - cell response function P plotted in panel b.

For curve E_1

$w=g_{H.A}(z:D_1).\pi(z)$ and the area under E_1 is $\mu_{E.A}(D_1)$ or $I_{E.A}(D_1)$

For curve E_2

$w=g_{H.A}(z:D_2).\pi(z)$ and the area under E_2 is $\mu_{E.A}(D_2)$ or $I_{E.A}(D_2)$

Panel d: Corresponds to panel c but for radiation of quality B.

Curve F_1 and F_2 represent the effect incidence density functions

$w=g_{H.B}(z:D_1).\pi(z)$ and the area under F_1 is $\mu_{E.B}(D_1)$ or $I_{E.B}(D_1)$; and

$w=g_{H.B}(z:D_2).\pi(z)$ and the area under F_2 is $\mu_{E.B}(D_2)$ or $I_{E.B}(D_2)$

The fraction of hits which result in the all-or-none effect will be termed 'the hit effectiveness ratio' and designated as ε with subscript to indicate the quality it refers.

Thus

$$\epsilon_A = \int_{z_o}^{\hat{z}_A} f_A(z) \cdot \pi(z)\, dz$$

and $$\epsilon_B = \int_{z_o}^{\hat{z}_B} f_B(z) \cdot \pi(z)\, dz$$

From the definition of ε,

$$I_{E.A}(D) = \varepsilon_A . \mu_{H.A}(D)$$

where $I_{E.A}(D)$ is the fraction of hit cell which result in all-or-none effect.

$\mu_{H.A}(D)$ is given by:

$$\mu_{H.A}(D) = D/(\bar{z}_A)$$

So $I_{E.A}(D) = D.\ \varepsilon_A/(\bar{z}_A)$; and

$$I_{E.B}(D) = D.\varepsilon_B\ /(\bar{z}_B)$$

where $\bar{z}_A$ and $\bar{z}_B$ are the mean hit size for radiation quality A and B respectively.

The incidence of the all-or-none effect can be expressed in a very simple form, namely:

$$I_{E.A}(D) = D.\ \varepsilon_A/(\bar{z}_A);\ \text{and}$$

$$I_{E.B}(D) = D.\varepsilon_B\ /(\bar{z}_B)$$

The relative biological effectiveness (RBE) of quality B relative to A, according to the definition of RBE, is given by:

$$RBE(B/A) = [\varepsilon_B\ /(\bar{z}_B)]\ /\ [\varepsilon_A/(\bar{z}_A)]$$

$$= [\varepsilon_B\ /\ \varepsilon_A].[\bar{z}_A\ /\ \bar{z}_B]$$

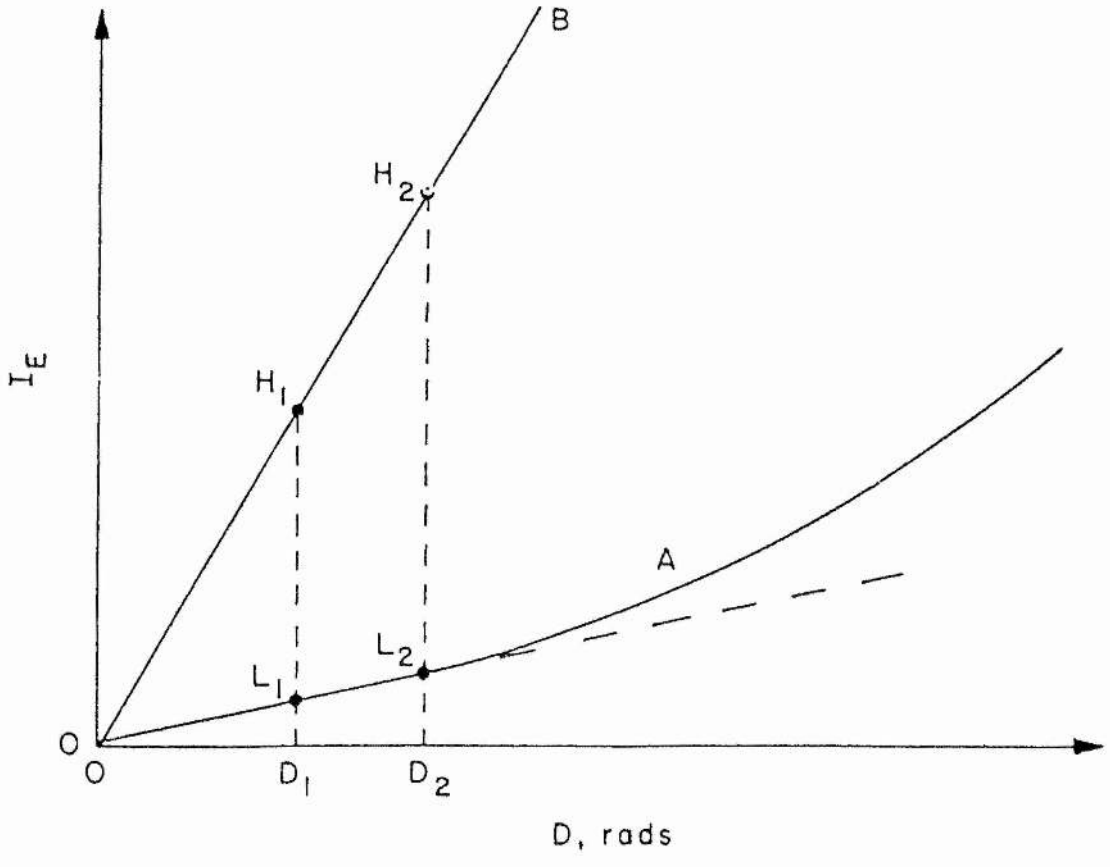


Fig. 2.7: Schematic plots of the expected incidence I_E of the all-or-none effect vs. the amount of radiation, D for qualities A and B. The amounts D_1 and D_2 are shown as being in the linear range for both curves. The ordinates of the points L_1 and L_2 are equal to the areas under curves E_1 and E_2 in panel c of figure 2.6, and the ordinates of points H_1 and H_2 are equal to the areas under curves F_1 and F_2 in panel d of figure 2.6. The incidence I_E equals the risk per undosed cell (as opposed to the ordinate p in panel b of figure 2.6, which is the risk per dosed cell).

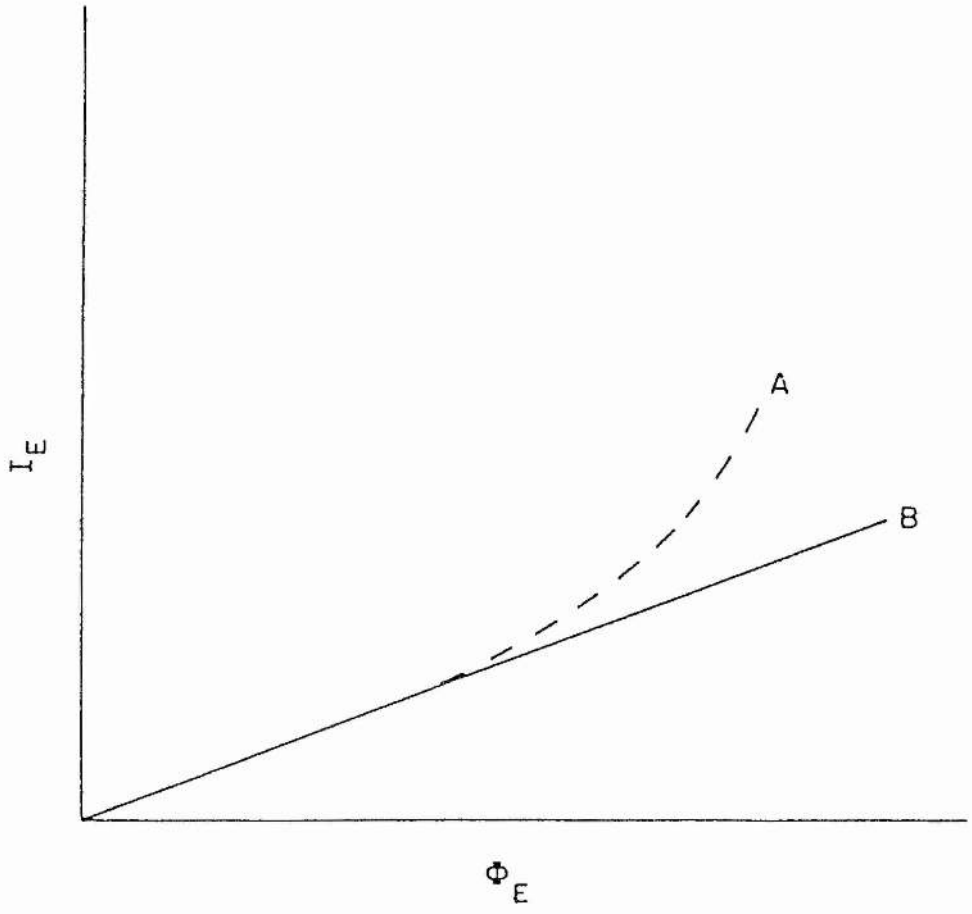


Fig. 2.8: The expected incidence I_E vs. the amount of radiation measured as effective fluence ϕ_E, i.e. the number of charged particles per unit area capable of producing the all-or-none effect. Curve A is for a high- and curve B for a low fluence rate.

2.4.4.3. Survival Equation

If $I_{E,A}(D)=D.\varepsilon_A/(\bar{z}_A)$ is the mean number of cells hit (i.e. incidence), after given dose D of radiation with quality A, then the Survival Fraction (SF) for this model is given by:

$$SF=\exp(-I_E) = \exp(-D.\varepsilon_A/(\bar{z}_A)) \text{ or } \ln SF=-I_E = -D.\varepsilon_A/(\bar{z}_A)$$

where

I_E is the fraction of hit cells which result in all-or-none effect or the incidence of the all-or-none effect after given dose D, can be expressed by the following term:

$$I_{E,A}(D)=D.\ \varepsilon_A/(\bar{z}_A)$$

For radiation of quality A, the survival equation is:

$$\ln SF=-\ D.\varepsilon_A/(\bar{z}_A)$$

The general form for I_E is given by:

$$I_E =\alpha D + \beta D^2 + \gamma D^3 + ...$$

For low level radiation exposure (LLE) only the linear term is significant due to the fact that there is a complete repair of sub-effect damage before a second cell dose is delivered. It is expected that even with high level radiation (HLR) exposure, terms higher than the square would rarely ever be detected.

The survival equation for the HSE model is given by:

$$\text{Ln SF} = -mD$$

where

m is the gradient which depends on the LET of the radiation, which is also equal to $m=\varepsilon_A/(\bar{z}_A)$ for radiation quality A.

2.4.4.4. Model Appraisal

i. If hit size z, is the most important parameter, irrespective of radiation type, the same hit size from figure 2.6 (page 63), could give rise to different effects. Both z, are the same. Suppose that the critical volume is DNA double strand. In the first case, four DNA segments are affected by z, whereas in the second case, three DNA segments are affected by z. What matters most is the spacing and correlation (orientation) of energy deposition events. If it is correlated with a DNA dsb (sensitive segment), the effect would be more than if it is not correlated with a DNA segment.

ii. The derivation of the hit size effectiveness function (HSEF) is complicated and requires the availability of accurate data on a number of radiations of different LET. How can we test the HSEF independently? May be independent testing is not feasible due to the fact that the hit sizes received by the exposed cells are governed by stochastic processes and in order to compare the probabilities, a lot of accurate data on all-or-none effects are required.

iii. The definitions of LLR (i.e. average $I_H << 1$) and HLR ($I_H >> 1$) are not very critical because when every single track counts, the λ (spacing between primary ionizations) is important.

It is stated by Weber [108] that the HSE approach is a direct application of microdosimetry to low exposure irradiation, in which only a small proportion of the exposed cells are hit predominantly by single tracks, in a cell population. The HSE approach can be regarded as a microdosimetric version of hit-theory by using a continuous function (HSEF) instead of a step function (i.e. 0 and 1) for the response. The term 'hit' denotes the total amount of energy transferred to the proposed sensitive structure. At low doses the 'hit' varies widely from zero to a maximum value, depending on hit size (radiation quality). In classical hit-theory, a hit size effectiveness (ε_j) is equal to:

i. zero ; for all hit multiplicities smaller than n; and

ii. one ; for all hit multiplicities equal to or bigger than n.

The survival fraction (SF), when fixed hit sizes are assumed, is expressed by the following equation:

$$SF = \exp(-\lambda D) \sum_{j}^{max} (1-\epsilon_j) \frac{(\lambda D)^j}{j!}$$

where D is the radiation dose.

From hit-target theory, it is given that:

$$p(j) = \exp(-\lambda D) \cdot \frac{(\lambda D)^j}{j!}$$

and survival fraction (SF) is given by:

$$SF = \frac{N}{N_o} = \sum_{j=0}^{n-1} p(j)$$

In the HSE model by Bond and Varma, a probability distribution of hit sizes for a given dose replaces the Poisson distribution of hit theory.

2.4.4.5. Testing Bond and Varma's model

To test his model, Bond used various data which includes the following:

i. Data for induced pink mutations in Tradescantia produced by x-ray irradiation, which have a slope of unity and are in good agreement with experimental data up to a dose of about 0.1 Gy [108][109][110][111];

ii. The production of chromatid exchanges in CH2B2 cells after exposure to various heavy ions and x-rays [108][112].

2.4.5. Track Core (TC) Model (Watt)

2.4.5.1. Introduction

A track core model of radiation action by Watt [113] has been evolved directly from experimental observation of biological irradiations. It uses the interaction spacing concept, namely the mean free path of primary ionization along the primary track λ, as a basis. It is known that the radiation damage is initiated by the charged particle tracks [114] and the single-valued parameter which determines quality is the linear primary ionisation of the charged particles. It is important to realise that the λ emerges from the study of the cellular data, based on laboratory experimental radiobiology; it is the parameter which best unifies the data for a wide range of radiation types and end-points. In deriving the model, the following assumptions and deductions are made:

i. Single track direct action is dominant at medium and low doses. Indirect (radical) action is deduced to be relatively small;

ii. There is no temperature dependence on the effect cross-section; and

iii. Results are for asynchronous cells: there is no specific allowance for variations in radiosensitivity during the cell cycle.

A mammalian cell contains DNA in its nucleus and double-strand breaks in the DNA are identified from the experimental analyses as the critical lesion. The traversal of a charged particle along a mean chord through the cell nucleus will activate the number of overlapping DNA segments at risk, subject to the range of the particle. What matters most, is the number of induced DNA dsb due to the charged particle traversal. Absolute biological effectiveness (ABE) is obtained and expressed as an effect cross-section in this model to indicate the effectiveness of a particular radiation to induce DNA dsb in any specified biological cellular system.

2.4.5.2. Basic principle

In a population of cells irradiated by either directly or indirectly ionising radiation, the relevant charged particles will interact with the cells. The critical lesions considered in this model is the DNA double strand break (dsb). The yield of DNA double strand breaks (dsb) is derived from the following processes [114]:

2.4.5.2.1. Direct Action

The cross section for DNA dsb production is given by:

$$\sigma_d=\sigma_g.n_o.\varepsilon$$

where

σ_g the projected geometrical area of the DNA ($\sigma_g \approx 4\ \mu m^2$):

n_o the number of overlapping segments at risk along a mean chord through the cell nucleus; and

ε the probability that at least a single interaction will occur in each of the two strands, each of thickness x, spaced at a mean chord distance.

The probable values of ε are:

i. For two ionisations occurring anywhere in the 2 nm distance i.e. $\varepsilon=[1-(1+\lambda_o/\lambda)\exp(-\lambda_o/\lambda)]$;

ii. For one ionisation occurring in the first strand and the second, within the next 2 nm distance i.e. $\varepsilon=[1-\exp(-x/\lambda)][1-\exp(-\lambda_o/\lambda)]$; and

iii. For non-saturating tracks, one hit in each of the two strands and nothing in between

i.e. $\varepsilon=\exp(-\lambda_o/\lambda)[1-\exp(-x/\lambda)]^2$.

The mean number of DNA dsb induced per cell by direct action is given by:

$$N_{D,dsb}=\sigma_d\phi$$

where

ϕ is the integral equilibrium charged particle fluence in the cell nucleus; and $\sigma_d=\sigma_g.n_o.\varepsilon$

2.4.5.2.2. Indirect Action

The mean number of DNA dsb produced per cell by radical action is given by:

$$N_{I,dsb}=n_t.\sigma_{dsb}.\phi$$

and $\sigma_{dsb}=\sigma^2_{ssb}/\sigma_g$

where

σ_{ssb} is the production cross section of single strand breaks in DNA, the general form is given by: $\sigma_{ssb}=a_1.\exp(-a_2.C_{sc})[1-\exp(-a_3.\bar{L}_T/C_{DNA})]$

a_1 is a geometrical interaction cross section:

a_2, a_3 are constants;

C_{sc} is the intranuclear scavenging concentration;

C_{DNA} is the molecular density of single strands of DNA present in the cell nucleus; and

$\bar{L}_T$ is the track average LET for the equilibrium of the charged particles in the cell nucleus; and

n_t is the total number of DNA segments in the whole cell nucleus which differs with n_o.

2.4.5.2.3. Mixed Radiation

For mixed radiation the combined effects of indirect and direct actions on individual strands gives:

$$\sigma_{M,dsb} = 2 . n_o . [1 - \exp(-x/\lambda)] . \frac{\sigma_{ssb}}{\sigma_g}$$

$$N_{M.dsb} = \sigma_{M.dsb} . \Phi$$

and $N_{T.dsb} = N_{D.dsb} + N_{I.dsb} + N_{M.dsb}$

The repair of indirect and direct damage is assumed to occur at the same rate with a mean repair time t_{rep}. A simple time-dependent damage factor can be derived as follows:

$$K(t_i) = \frac{1}{t_i} . \int_0^{t_i} \exp[-(t_t - t)/t_{rep}] \, dt$$

The overall survival fraction (SF) for an irradiation of a population of cells is given by:

$$SF = \exp[-N_{T.dsb} . K(t_i)].$$

If the repair factor is considered to be 100 percent, the SF is given by:

$$SF = \exp[-N_{T.dsb}].$$

SF can also be expressed in terms of the absolute biological effectiveness (ABE) as follows:

$$SF = \exp(-ABE . \phi)$$

where

ABE is the mean number of double strand breaks per unit incident fluence of primary radiation; and

ϕ is the incident fluence of primary radiation.

2.4.5.8. Model Appraisal

The approach used in deriving the model is to correlate on a single curve the reported information on cellular effects observed in a variety of irradiation circumstances, for many radiation types and for a variety of biological end-points (refer to figure 4.1). The model is classified as a phenomenological model.

Of the five main biophysical models which have been explained in brief so far, this is the only model which uses interaction (event) spacing λ, as the physical parameter to specify radiation. This is a significant development conceptually and can be used as an effective means of specifying radiation quality. The following explanation on the signal to background ratio of effectiveness if dose is used, provides justification on using λ as radiation specifier:

> Double strand break (dsb) is considered as the most important lesion induced by the radiation in the cellular DNA. From radiochemistry it is known that only about 8 eV is required to rupture sufficient chemical bonds to produce a dsb. The distance between DNA strands is about 2 nm. If energy deposition parameter is used in this case take for example at just below the maximum RBE-LET curve, for any typical end-points, in the energy region generally considered to be unsaturated, α particle expends about 110 kev/μm, whereas a proton expends only about 60 kev/μm to produce the same effect. For a 2 nm distance (equivalence to 2×10^{-3} μm), the mean energy expended by alpha and proton are respectively 220 ev and 120 ev. The signal to noise ratio for alpha and proton are respectively 7% and 4%. For low LET, the corresponding ratio is in the order of 0.003%. Therefore it seems inappropriate to use energy deposition parameters of any kind for the interpretation of radiation effect because the small changes can not be accurately quantified against the large signal to noise ratio.

2.4.5.9. Testing Watt's model

Extensive data of cell survival were used [115][116] to test the model, which include the following:

i. The ^{60}Co γ irradiations of HeLa cells by Hall and Bedford 1964 [117];

ii. The dose survival data for irradiations of mouse embryo fibroblasts with fission neutron E_n=0.85 MeV by Hill et-al in 1982 and 1984 [118][119]; and

iii. The irradiation with alpha particles (2.7 MeV) by Hieber et-al in 1987 [120].

The overall result is satisfactory and detail discussion is given by Watt [135].

2.5. Test and Inter-comparison of Models

There are a few ways to inter-compare biophysical models which include the following:

First, from the survival fraction equations, separate the terms which consist of Dose (D) or ϕ at one side and the terms which do not consist of D or ϕ at the other side. Then plot the graph against D or ϕ for each of the models i.e. display on a unified plot. Any deviation in the unified plot, indicates differences. This procedure could be difficult to carry out if the model is a complex mathematical expression;

Second, by using standard sets of bench mark data, curve fit each model and determine the error. Inter-compare the errors for each model. However this exercise requires a lot of data points for various types of radiation which are available (i.e. published data). Furthermore the modeller may have carried out this procedure in the development of the model; or

Third, by applying mathematical treatments to emphasise model characteristics, such as comparing the values of the first derivative against dose (D) or fluence (ϕ). This procedure can be repeated for each model and for inter-comparison purposes, the results could be displayed in a same graph.

In this thesis the first and the third methods are carried out on the five main biophysical models of radiation action and the results are shown in table 2.4. Inter-comparison of the five main biophysical models is carried out by:

(i) determining for each model the initial slope (i.e.dlnS/dϕ when $\phi \rightarrow 0$), the final slope (i.e. dlnS/dϕ when $\phi \rightarrow \infty$), the number of parameters and their meanings, the basis of the model such as critical target, lesions types and the principle used; and

(ii) determining the first derivative of each ln survival curve against D and ϕ, and display the results on the same graph.

2.5.1. LPL Model (Curtis)

The survival equation is given by:

$$lnS = -(\eta_L + \eta_{PL})D + \epsilon \ln\left[1 + \frac{\eta_{PL}}{\epsilon} D\left[1 - \exp(-\epsilon_{PL} t_r)\right]\right]$$

$$lnS = -(\eta_L + \eta_{PL})\,\Phi\,\bar{L}_T + \epsilon\,\ln\left[1 + \frac{\eta_{PL}}{\epsilon}\Phi\,\bar{L}_T\left[1-\exp\left(-\epsilon_{PL}t_r\right)\right]\right]$$

where:

η_L is the rate of L lesion production per unit absorbed dose;

η_{PL} is the rate of PL lesions production per unit absorbed dose; ε_{PL} is the rate of correct repair for PL lesion per unit time;

ε_{2PL} is the rate of binary misrepair for PL lesion per unit time;

$$\epsilon = \frac{\epsilon_{PL}}{\epsilon_{2PL}}$$

and t_r is the repair time.

Assume that all parameters are not a function of ϕ or D.

$$\frac{dlnS}{dD} = -(\eta_L + \eta_{PL}) + \epsilon\,\frac{\left[\frac{\eta_{PL}}{\epsilon}\left[1-\exp\left(-\epsilon_{PL}t_r\right)\right]\right.}{\left[1+\frac{\eta_{PL}}{\epsilon}D\left(1-\exp\left(-\epsilon_{PL}.\,t_r\right)\right)\right]}$$

$$\frac{dlnS}{d\Phi} = -(\eta_L + \eta_{PL})\,\bar{L}_T + \frac{\left[\eta_{PL}\bar{L}_T\left[1-\exp\left(-\epsilon_{PL}t_r\right)\right]\right.}{\left[1+\frac{\eta_{PL}}{\epsilon}\Phi\,\bar{L}_T\left(1-\exp\left(-\epsilon_{PL}.\,t_r\right)\right)\right]}$$

i.e. Using equation $D=L\phi$; and

$d/d\phi=(d/dD).(dD/d\phi)$ or $d/d\phi=L.(d/dD)$;

i. The initial slope

When $D\to 0$:

$$\frac{dlnS}{dD} = -(\eta_L)\left[1+\exp\left(-\epsilon_{PL}t_r\right)\right]$$

When $\phi\to 0$:

$$\frac{dlnS}{d\Phi} = -\bar{L}_T\left[\eta_L + \eta_{PL}\exp\left(-\epsilon_{PL}t_r\right)\right]$$

ii. The final slope

When D→∞:

$$\frac{dlnS}{dD} = -(\eta_L + \eta_{PL})$$

When $\phi \rightarrow \infty$:

$$\frac{dlnS}{d\phi} = -(\eta_L + \eta_{PL})\,\bar{L}_r$$

iii. Number of parameters and their meanings

Five independent parameters are used in the LPL model. η_L and η_{PL} indicate the production rate of L lesions and PL lesions respectively per unit absorbed dose. L lesion is assumed irreparable and more severe than PL lesion which can be either repaired correctly or binary mis-repaired to become an L lesion. ε_{PL} and ε_{2PL} indicate the rate of correct repair for PL lesions and the rate of binary misrepair for PL lesions respectively per unit time. The fifth parameter is t_r which is the repair time.

iv. Basis of the model

Dose is used to specify radiation quantity and the critical target is not specified but it is implicit that the lesions are in the DNA molecule; L and PL lesions. Interaction between PL lesions and repair of PL lesions are assumed to take place in this model.

2.5.2. PLI Model (Harder)

The survival equation is given by:

$$lnS = -\ln(n)\left[\exp\left(-\frac{D}{D_q}\right) + \frac{D}{D_q} - 1\right]$$

where

n is the extrapolation number (i.e. note that not all survival curves have an extrapolation number)

D is the Dose; and

D_q is the shoulder dose

$$\frac{d(lnS)}{dD} = -\frac{\ln(n)}{D_q}\left[1-\exp\left(-\frac{D}{D_q}\right)\right]$$

$$\frac{d(lnS)}{d\Phi} = -\frac{\ln(n)}{\Phi_q}\left[1-\exp\left(-\frac{\Phi}{\Phi_q}\right)\right]$$

i. The initial slope

When $\phi \to 0$: $\frac{dlnS}{dD} = 0$

When $\phi \to 0$: $\frac{dlnS}{d\Phi} = 0$

ii. The final slope

When $\phi \to \infty$: $\frac{dlnS}{dD} = -\frac{\ln n}{D_q}$

When $\phi \to \infty$: $\frac{dlnS}{d\Phi} = -\frac{\ln n}{D_q} \cdot \overline{L_1}$

iii. Number of parameters and their meanings

Two parameters are used in the PLI model. n and D_q indicate the extrapolation number (corresponding to the number of targets in the multi-target single hit model) and the shoulder dose D_q, (the quasithreshold dose) which corresponds to the width of the shoulder, respectively.

iv. Basis of the model

The basis of the PLI is pairwise interaction between primary lesions. The critical target is assumed to be at contact regions, namely the regions with contact between different chromatin fibres or between sections of the same fibres. Radiation induced primary (i.e. molecular) lesions are assumed to occur in the contact regions which are able to interact pairwise. Dose is used to specify radiation quantity.

2.5.3. The CTS Model (Katz)

The survival equation is given by:

$$lnS = -\frac{\sigma D}{L} + \ln\left(1-\left[1-\exp-\left((1-P)\frac{D}{E_o}\right)\right]^m\right)$$

where

m is the target multiplicity or the extrapolation number;

E_o is the critical Dose or the extrapolated D_γ^{37};

σ_o is the saturation cross-section found at a value of

$z^2/\kappa\beta^2=4$;

κ relates to the size of the sensitive container which corresponds to the value of σ_o at $z^2/\kappa\beta^2=4$.

A set of parameters of Katz's model for cell inactivation is given by σ_o, E_o, κ, m.

$$\frac{dlnS}{dD} = -\frac{\sigma}{L} + \frac{\frac{d}{dD}\left[1-\exp-\left((1-P)\frac{D}{E_o}\right)\right]^m}{\left(1-\left[1-\exp-\left((1-P)\frac{D}{E_o}\right)\right]^m\right.}$$

$$\frac{dlnS}{dD} = -\frac{\sigma}{L} - \frac{m\frac{(1-P)}{E_o}\exp-\left(\frac{(1-P)D}{E_o}\right)\left[1-\exp-\left((1-P)\frac{D}{E_o}\right)\right]^{m-1}}{\left(1-\left[1-\exp-\left((1-P)\frac{D}{E_o}\right)\right]^m\right)}$$

$$\frac{dlnS}{d\phi} = -\sigma - \frac{mL\frac{(1-P)}{E_o}\exp-\left(\frac{(1-P)L\phi}{E_o}\right)\left[1-\exp-\left((1-P)L\frac{\phi}{E_o}\right)\right]}{\left(1-\left[1-\exp-\left((1-P)L\frac{\phi}{E_o}\right)\right]^m\right)}$$

i. The initial slope

When D→0: $\frac{dlnS}{dD} = -\frac{\sigma}{L}$

When $\phi \to 0$:

$$\frac{dlnS}{d\phi} = -\sigma$$

ii. The final slope

When $D \to \infty$:

$$\frac{dlnS}{dD} = -\frac{\sigma}{L} - \frac{(1-P)}{E_o}$$

When $\phi \to \infty$:

$$\frac{dlnS}{d\phi} = -\sigma - L\frac{(1-P)}{E_o}$$

iii. Number of parameters and their meanings

There are four parameters used in the CTS model by Katz, namely σ_o, E_o, κ and m. m is the target multiplicity, E_o is the critical dose, σ_o represents the size of the container and κ represents the critical target size in the container. Katz suggests that the targets in the container can be considered as beans in a bean bag. E_o and m are parameters for multi-target statistics to describe the response from gamma kill at low LET, whereas σ_o and κ are parameters for one hit statistics of ion kill at high LET.

iv. Basis of the model

The basis of the CTS model is the dose deposited by δ-rays, which inactivates sensitive sites along and around the particle tracks. The concept used is that the response to δ-rays (secondary electrons) follows the same functional form for γ-rays and for the δ-rays surrounding an ion's path. z^2/β^2 is used to indicate the δ-ray yield per unit track length. No specific biological structure or damage type are inferred as the critical target or lesion in this model.

2.5.4. HSE Model (Bond and Varma)

In low level radiation exposure, the survival equation is given by:

$$\ln SF = -mD$$

The first derivative of lnSF against Dose D, is given by:

$$\frac{d(LnSF)}{dD} = -\alpha$$

The first derivative of lnSF against fluence (ϕ), is given by:

$$\frac{d(LnSF)}{d\phi} = -\alpha \, . \, L$$

where

m is the linear coefficient which depends on the LET of the radiations, which is also equal to $m=\varepsilon_A/(\bar{z}_A)$ for radiation quality A. : and

D is the absorbed dose.

i. The initial slope:

When D→0: the slope → -m, which is determined by the LET (L) of the radiation.

When $\phi \rightarrow 0$: the slope → -mL .

ii. The final slope

When D→∞: the slope → -m i.e the same as the initial slope.

When $\phi \rightarrow \infty$: the slope → -mL i.e. the same as the initial slope.

iii. Number of parameters and their meanings

The product mD is equal to I_E, the expected incidence of a single cell effect, given by the following equation:

$$I_E = \frac{\epsilon}{\bar{z}} \, . \, D$$

where

ε is the hit effectiveness ratio i.e. the fraction of hits which result in the all-or-none effect;

$\bar{z}$ is the mean hit size.

iv. Basis of the model

The basis of this model is the amount of energy deposited in the critical volume of the irradiated cell, measured as a single event spectra in microdosimetry. However the spectra needs to be multiplied by a function (HSEF) which provides the probability that a cell with a certain hit size (cell dose) will manifest the all-or-none effect. The product, I_E is the incidence of the all-or-none effect. Poisson statistics are assumed and consequently the survival fraction (SF) is calculated according to the formula $SF= \exp(-I_E)$. The critical target, within the cell nucleus, must be hit by a charged particle in order to have a non-zero probability of causing the all-or-none effect.

2.5.5. TC Model (Watt)

The survival equation is given by:

$$lnS = -ABE.\phi_{cp}$$

$$\phi_{cp} = N.\sigma_{tr}.\phi_{\gamma}$$

and

$$\phi_{eq} = N.\sigma_{tr}.\phi_{\gamma}.\overline{R}_r$$

where ABE is the probability to induce DNA double-strand breaks per unit incident fluence; ϕ_γ is the incident fluence; ϕ_{cp}, ϕ_{eq} is the charged particle fluence and the charged particle equilibrium fluence respectively; and R_r is the average range of the charged particles. ABE values are calculated according to the following equation:

$$ABE = (\sigma_g.n_o)(\phi_s.\epsilon)(N\sigma_{tr})k(t_i) + indirect\ component\ .$$

where

$\sigma_g.n_o$ is the projected cross-sectional area of DNA and n_o is the number of DNA double strands at risk;

$\phi_s.\varepsilon$ is the weighted integral equilibrium fluence of charged particle per unit incident fluence, and ε is the efficiency for the charged particles to induce DNA dsb;

$N.\sigma_{tr}$ is the mass transfer coefficient; and

$k(t_i)$ is the repair term which for simplification is assumed as one.

$$\frac{dlnS}{d\phi_{cp}} = -\phi_{cp}\frac{d(ABE)}{d\phi_{cp}} - ABE$$

i. The initial slope

When $\phi \to 0$; $$\frac{dlnS}{d\phi_{cp}} = -\phi_{cp}\frac{d(ABE)}{d\phi_{cp}} - ABE$$

Only single track effect is considered, at lower dose range;

$$\frac{dlnS}{d\phi_{cp}} = -ABE = -(\sigma_g.n_o)\left(\frac{R}{d}\right).\left(1-\exp\left(-\frac{\lambda_o}{\lambda}\right)\right)$$

with the following assumptions;

i. At low dose, only single track effect and less;

ii. no repair is assumed to take place; repair factor K(tr)=1 ; and

iii. indirect contribution is assumed to be negligible.

ii. The final slope

When $\phi \to \infty$; $\frac{d\ln S}{d\phi_{cp}} = -\phi_{cp}\frac{d(ABE)}{d\phi_{cp}} - ABE$

There is no final slope due to the fact that;

i. The repair factor K(tr) is continuously acting;

ii. In the high dose region, ϕ_{cp}^2 becomes significant;

iii. the curve keeps on curving with no final slope.

iii. Number of parameters and their meanings

In this model only ABE and fluence ϕ_{cp}, are used. However ABE is derived and calculated by using the following six parameters:

σ_g is the projected geometrical area of the DNA;

n_o is the number of overlapping segments at risk;

R is the mean range of charged particle track;

d is the mean chord length, of the cell nucleus;

λ_o is approximately equal to 2 nm; and

λ is the mean free path between the primary ionizations.

iv. Basis of the model

In the TC model only one type of lesion is assumed namely DNA dsb, which is induced by the radiation and acts as the precursor for various end-points such as cell inactivation, chromosome aberrations or mutations. The latter have different probabilities of occurence. The mean free path between the primary ionizations along the charged particle track is used as a basis for the model.

Table 2.4: General Summary of Five Main Biophysical Models of Radiation Action

Authors	Curtis (LPL)	Harder (PLI)	Katz (CTS)	Bond and Varma (HSE)	Watt (TC)
Models	Lethal and Potentially Lethal	Pairwise Lesion Interaction	Cellular Track Structure	Hit Size Effectiveness	Track Core (TC)
Dosimetry principle used	Dose in term of energy deposited locally attributable to different severity of lesions i.e. PL and L lesions	$L_{100,D}$ is used as the physical parameter of the radiation.	Dose due to delta rays (δ-rays) distributed radially along the particle track.	Microdosimetry principle is used to determine HSEF (Hit Size Effectiveness Function)	Mean free path λ for the primary ionization along the track core with maximum probability to induce DNA dsb when λ=2 nm.

Authors	Curtis (LPL)	Harder (PLI)	Katz (CTS)	Bond and Varma (HSE)	Watt (TC')
Parameters	η_L is the rate of L lesion production per absorbed dose; η_{PL} is the rate of PL lesion production per unit absorbed dose; ε_{PL} is the rate of correct repair for PL lesion per unit time; ε_{2PL} is the rate of binary misrepair for PL lesion per unit time; $\varepsilon = \varepsilon_{PL}/\varepsilon_{2PL}$; and t_r is repair time	n is the extrapolation number; and D_q is the shoulder dose	m is the extrapolation number i.e.target multiplicity, of γ rays survival curve; κ relates the size of the sensitive element (i.e. the bean) and it indicates the boundary between the cellular track width regime and the cellular grain-count regime; E_o is the critical dose or the extrapolated D_{37}^{γ} after γ irradiation; σ_o is the saturation cross section, which relates the size of the sensitive element container i.e. the bean bag. Its value is found at a value of $z^2/\beta^2=4\kappa$; and z^2/β^2 indicate the	I_E is the fraction of hit cell which result in all-or-none effect. In low level: I_E= mD where m is a constant (i.e. $m=\varepsilon_A/(\bar{z}_A)$ for radiation A, $\bar{z}_A$ is the mean hit size, and ε is the hit effectiveness ratio namely the fraction of hits which result in all-or-none effect).	λ is the mean free path for primary ionization (I).

Authors	Curtis (LPL)	Harder (PLI)	Katz (CTS)	Bond and Varma (HSE)	Watt (TC)
Critical Target	DNA double strand (ds)	DNA double strands in contact between different chromatin fibres or sections of the same fibres. The cell nucleus is assumed to contain a number of interaction regions, where the radiation induced molecular lesions may be produced, upon different chromosomes or different parts of the same chromosome.	It is called the sensitive site, in the nucleus of cell. The critical target diameter is assumed as a_o.	It is called the critical volume but its exact form is not defined anatomically. The critical volume is inside the cell with the apparent mean diameter or cross-section σ. The macromolecular target must reside in it.	The critical target is DNA double strand of 2 nm distance (i.e. only if DNA is present)

Authors		Curtis (LPL)	Harder (PLI)	Katz (CTS)	Bond and Varma (HSE)	Watt (TC)
Lesion or Damage		Both PL and L lesions are associated with DNA dsb with different degree of severity. PL lesion is less severe than L lesion. L lesion and PL lesion are from pre-lesion i.e.short-lived biochemical lesions with lifetime shorter than 1 sec. L lesions are produced when two or more pre-lesions are formed close together, in a short distance along the track.	DNA dsb in Chromatin fibres. Pairwise lesion interaction, can take place during the appropriate phase of the repair processes i.e. the pairwise interaction between the contact regions. Lesions are formed due to intra-track as well as inter-track actions.	Any target which has received E_o, due to δ-ray produced by the charged particle, along and surrounding the track, is considered as a hit. Single hit multi-target statistic is assumed for this model. Targets in the cell are considered as beans in a bean bag.	The tissue content of critical volume must be hit by a charged particle in order for the chance of an all-or-none alteration of the cell (a quantal response) to be other than zero. Quantal response refers to irreversible changes such as chromosome abnormalities and cell death, genetic or neoplastic cell transformation.	The ionization events spatially correlated with maximum probability to induce damage when the distance is like a template with the DNA double strand (2 nm)
Initial slope	S.F when D→ 0	$\eta_L[1+\exp(-\varepsilon_{PL}t_r)]$	0	σ/L	$m=\varepsilon_A/(\bar{z}_A)$	ABE/L

Authors		Curtis (LPL)	Harder (PLI)	Katz (CTS)	Bond and Varma (HSE)	Watt (TC)
	S.F when $\phi \rightarrow 0$	$L[\eta_L+\eta_{PL}\exp(-\varepsilon_{PL}t_r)]$	0	σ	mL	ABE
Final slope	S.F when $D \rightarrow \infty$	$\eta_L+\eta_{PL}$	$\ln(n)/D_q$	$\sigma/L+(1-P)/E_o$	m	ABE/L
	S.F when $\phi \rightarrow \infty$	$(\eta_L+\eta_{PL})L$	$L.\ln(n)/D_q$	$\sigma + L(1-P)/E_o$	mL	ABE

Authors	Curtis (LPL)	Harder (PLI)	Katz (CTS)	Bond and Varma (HSE)	Watt (TC)
General Notes	The amount of energy deposition in DNA dsb is used to determine the severity of the lesions: PL lesion is less severe than L lesion.	The end-points considered in Harder's model are: i.the exchange type chromosome aberration: and ii. the reproductive cell death.	Effects produced by gamma and heavy charged particle irradiation are assumed due to the δ-ray dose along and surrounding the particle track.	HSEF is the function that provides the fraction of hit cells that respond quantally at each hit size. It combines hit theory and microdosimetry approaches.	The Track Core model employs mean free path (λ) concept, Mean free path emerges from the cellular data, as a parameter which best unifies data. Radiation effect is believed to depend mainly on the frequency and spatially correlated events with maximum effect when λ is equal to 2 nm.
	The followings parameters are commonly used to characterize survival curves of specified biological end-points against dose: i. The initial slope i.e. when $D \rightarrow 0$; ii. The final slope i.e. when $D \rightarrow \infty$; iii. D_o, D_{37} or ϕ_{37} i.e. the dose or fluence, required to reduced survival fraction to 1/e; or radiosensitivity.				

The summary for equations of survival fraction (SF) of each biophysical models of radiation action are given as follows:

i. For LPL Model (Curtis):

$$lnSF=-(\eta_L+\eta_{PL})D+\epsilon\ \ln\left[1+\frac{\eta_{PL}}{\epsilon}D[1-\exp(-\epsilon_{PL}t_r)]\right]$$

$$lnSF=-(\eta_L+\eta_{PL})\Phi\bar{L}_T+\epsilon\ \ln\left[1+\frac{\eta_{PL}}{\epsilon}\Phi\bar{L}_T[1-\exp(-\epsilon_{PL}t_r)]\right]$$

and $$\frac{dlnSF}{d\Phi}=-(\eta_L+\eta_{PL})\bar{L}_T+\frac{[\eta_{PL}\bar{L}_T[1-\exp(-\epsilon_{PL}t_r)]}{[1+\frac{\eta_{PL}}{\epsilon}\Phi\bar{L}_T(1-\exp(-\epsilon_{PL}.t_r))]}$$

ii. For PLI Model (Harder):

$$lnSF=-\ln(n)\ (\exp(-\frac{D}{D_q})+\frac{D}{D_q}-1)]$$

$$\frac{d(lnSF)}{d\Phi}=\frac{\ln(n)}{\Phi_q}[\exp(-\frac{\Phi}{\Phi_q})-1]$$

iii. For CTS Model (Katz):

Survival Fraction (SF) is given by: $SF=\Pi_i.\Pi_\gamma$ where Π_i is the ion-kill mode survival probability; and Π_γ is the gamma-kill mode survival probability.

In the Grain Count Regime: $\Pi_i=\exp(-\sigma\phi)$ or $\Pi_i=\exp(-\sigma D/L)$, where σ can be derived from $\sigma/\sigma_o=P=[1-\exp-(z^{*2}/\kappa\beta^2)]^m$.

$\Pi_\gamma=1-[1-\exp-(1-P)D/E_o]^m$.

Survival Fraction SF in the grain count regime is given by:

$SF=\exp(-\sigma\phi)\{1-[1-\exp-(1-P)D/E_o]^m\}$.

In the Track Width Regime: the gamma-kill mode survival probability is equal to one; $\Pi_\gamma=1$; and the ion-kill mode survival probability is given by; $\Pi_i=\exp(-\sigma\phi)$;

Survival Fraction SF in the track width regime is given by:

$SF=\exp(-\sigma\phi)$.

iv. For HSE Model (Bond & Varma):

The survival fraction (SF), is given by the following equation:

SF=exp(-mD)

where m is the gradient which depends on the LET of the radiation, which is also equal to $m=\varepsilon_A/(\bar{z}_A)$ for radiation quality A; and D is radiation dose; and

v. For TC Model (Watt):

$$SF=\exp(-ABE.\phi)$$

$$\ln SF=-ABE.\phi$$

where ABE is the Absolute Biological Effectiveness; and ϕ is the relevant charged particle fluence. The first derivative of SF against ϕ is given by:

$$\frac{d\ln SF}{d\phi}=-ABE$$

2.6. Conclusions

2.6.1. Intercomparison Based on Theoretical Approach

The results of the inter-comparison between the five main biophysical models are listed in table 2.4. The graphical illustrations for each model; its first derivative against dose D and Fluence ϕ, are given in:

i. Figures 2.9(a) and 2.9(b), for LPL model (Curtis);

ii. Figures 2.10(a) and 2.10(b), for PLI model (Harder);

iii. Figures 2.11(a) and 2.11(b), for CTS model (Katz);

iv. Figures 2.12(a) and 2.12(b), for HSE model (Bond and Varma); and

v. Figures 2.13(a) and 2.13(b), for TC model (Watt).

The overall graphical illustration for all models is given in figure 2.14. The parameters of the models in figure 2.14 are listed in table 2.5.

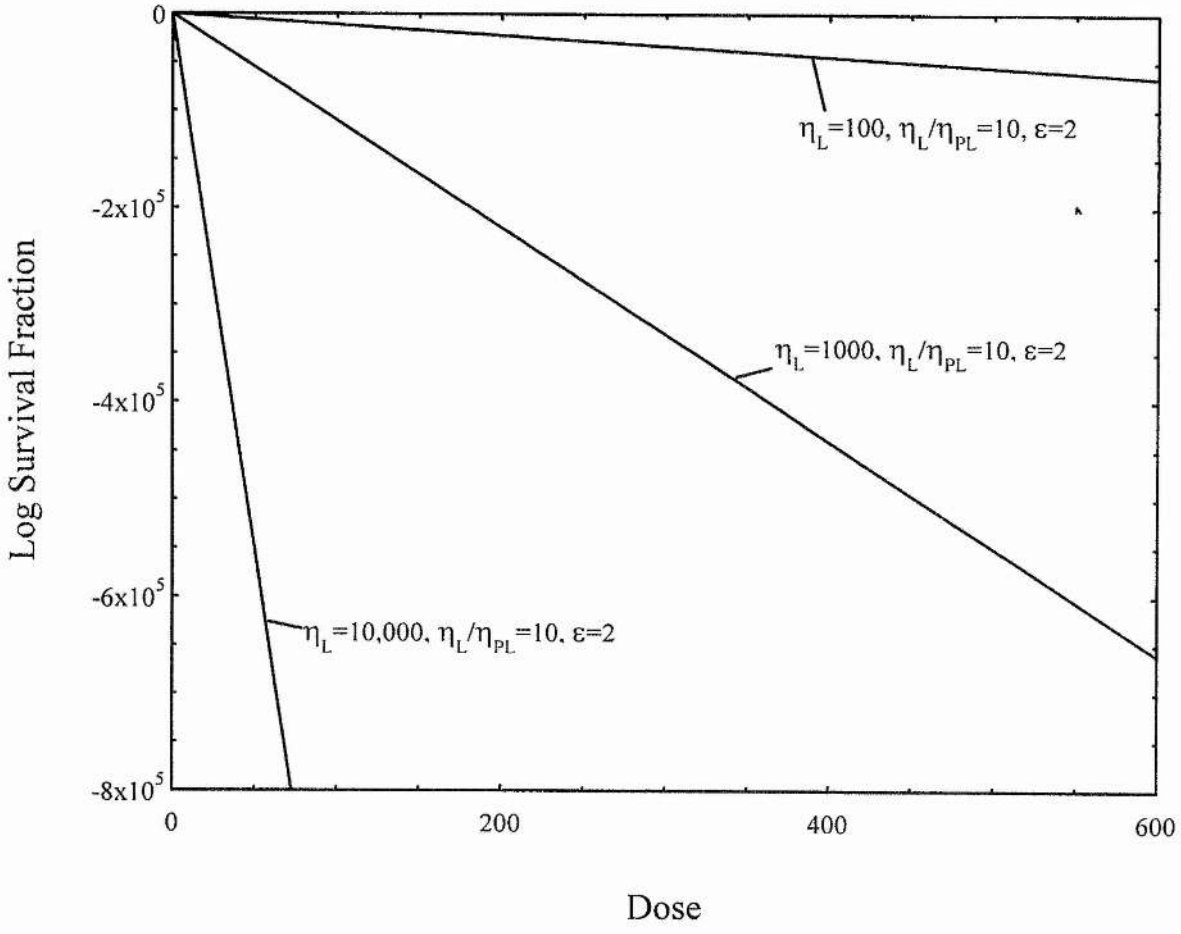


Fig. 2.9(a): LPL Model by Curtis: Log Survival Fraction (SF) against Dose, D

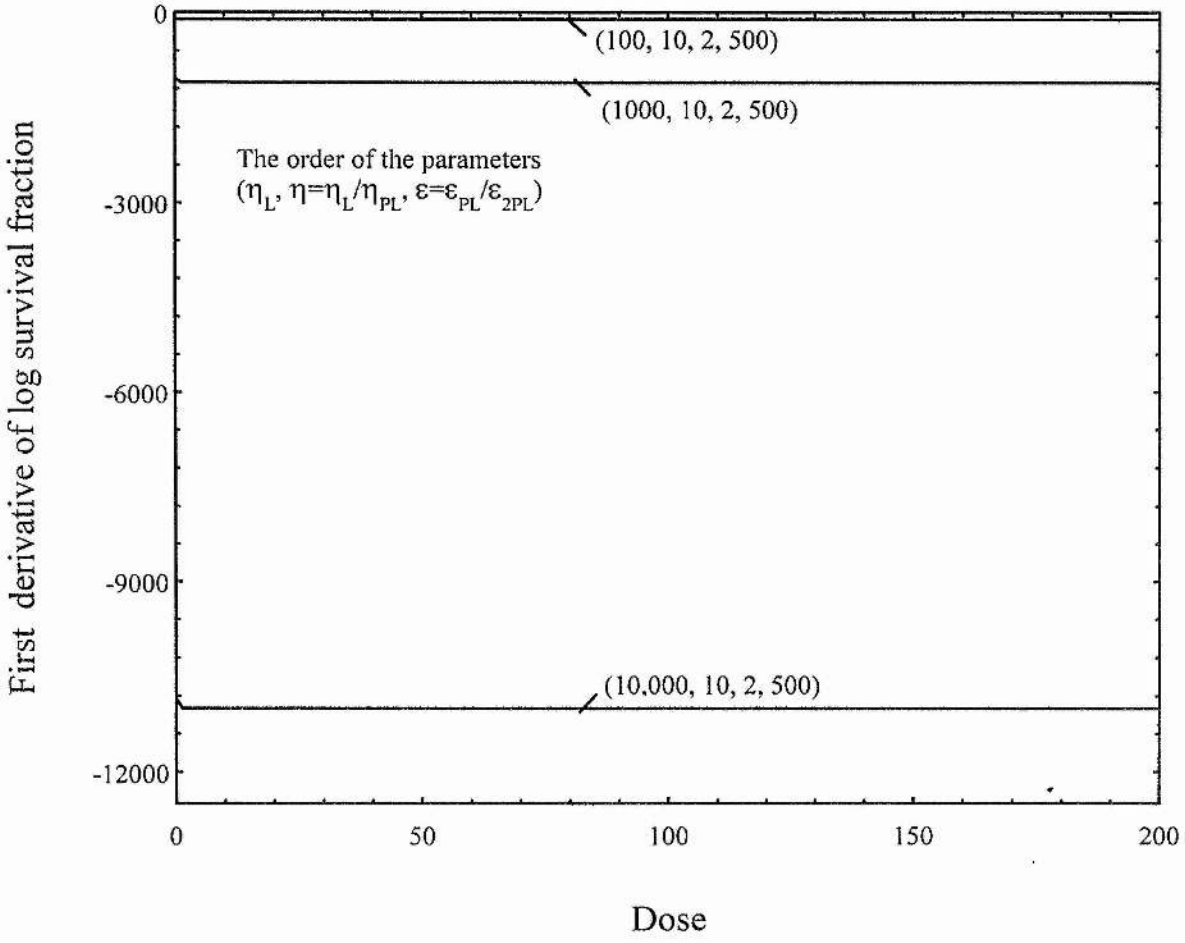


Fig. 2.9(b): LPL Model; First Derivative of Log Survival Fraction (SF) against Dose, D

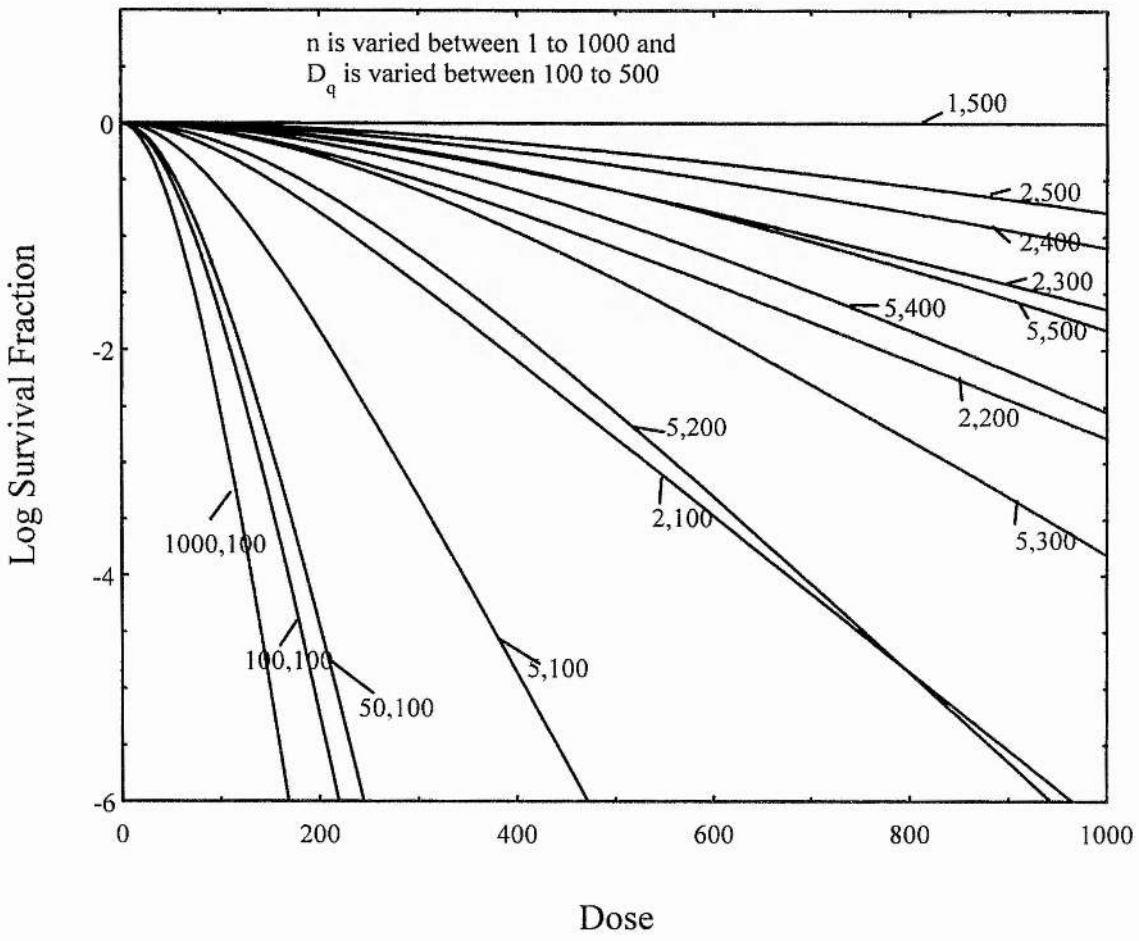


Fig. 2.10(a): PLI Model (Harder); Log Survival Fraction (SF) against Dose, D

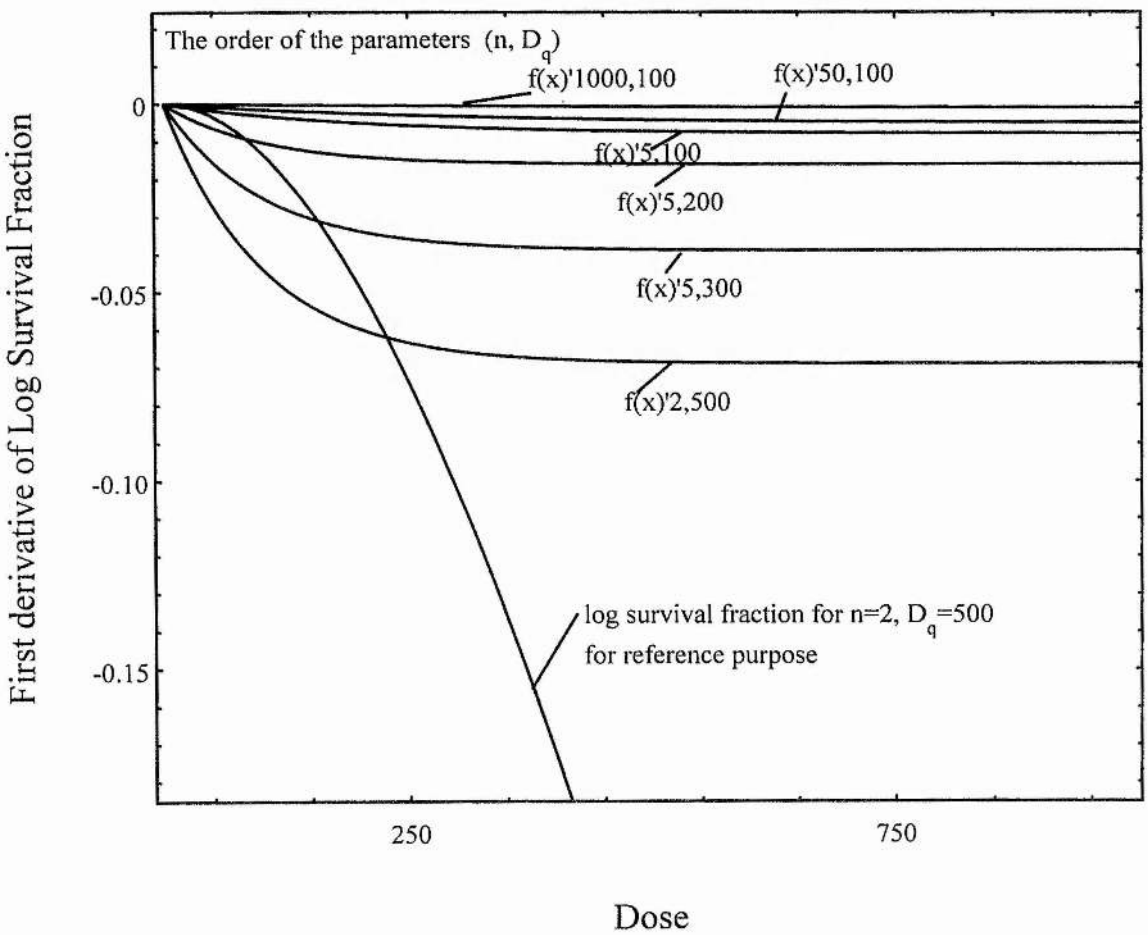


Fig. 2.10(b): PLI Model; First Derivative Log Survival Fraction (SF) against Dose, D

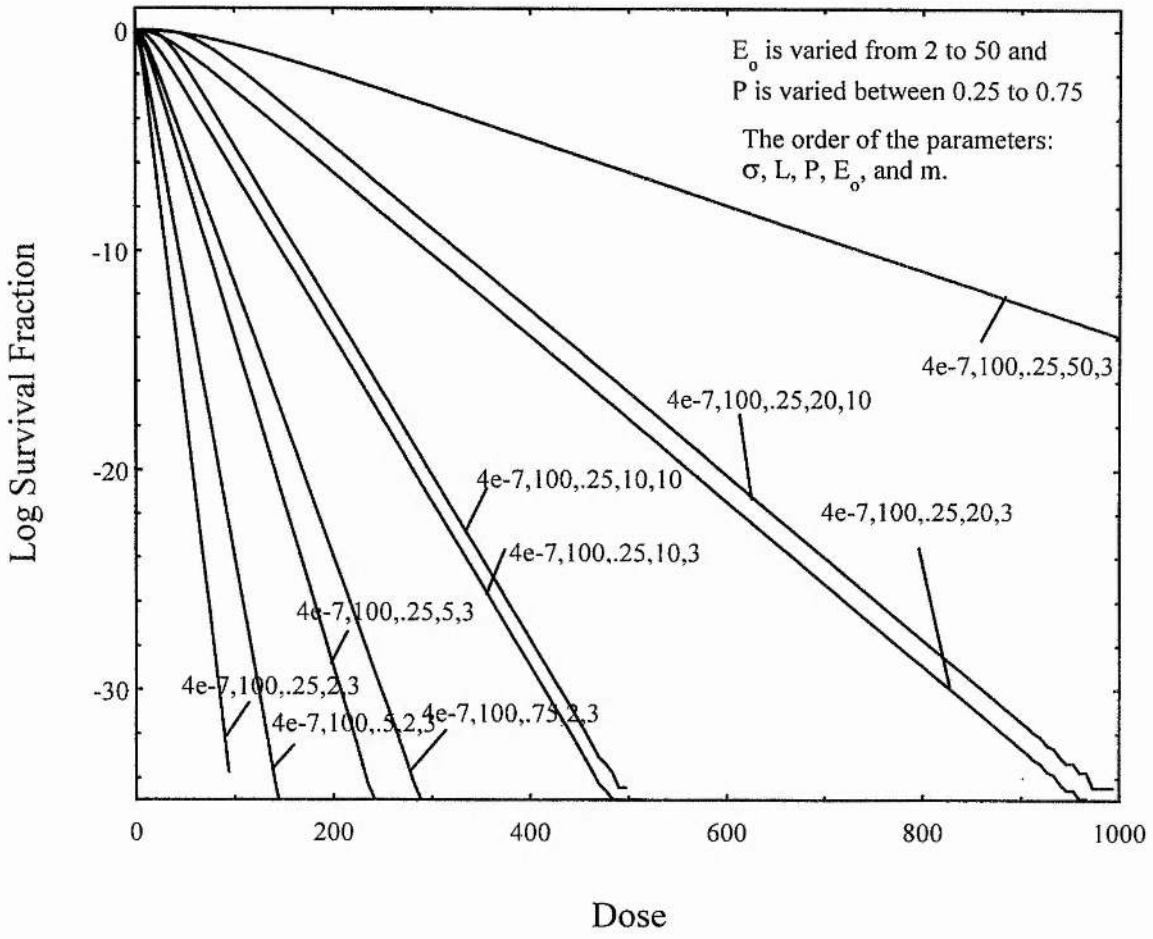


Fig. 2.11(a): CTS Model (Katz); Log Survival Fraction (SF) against Dose, D

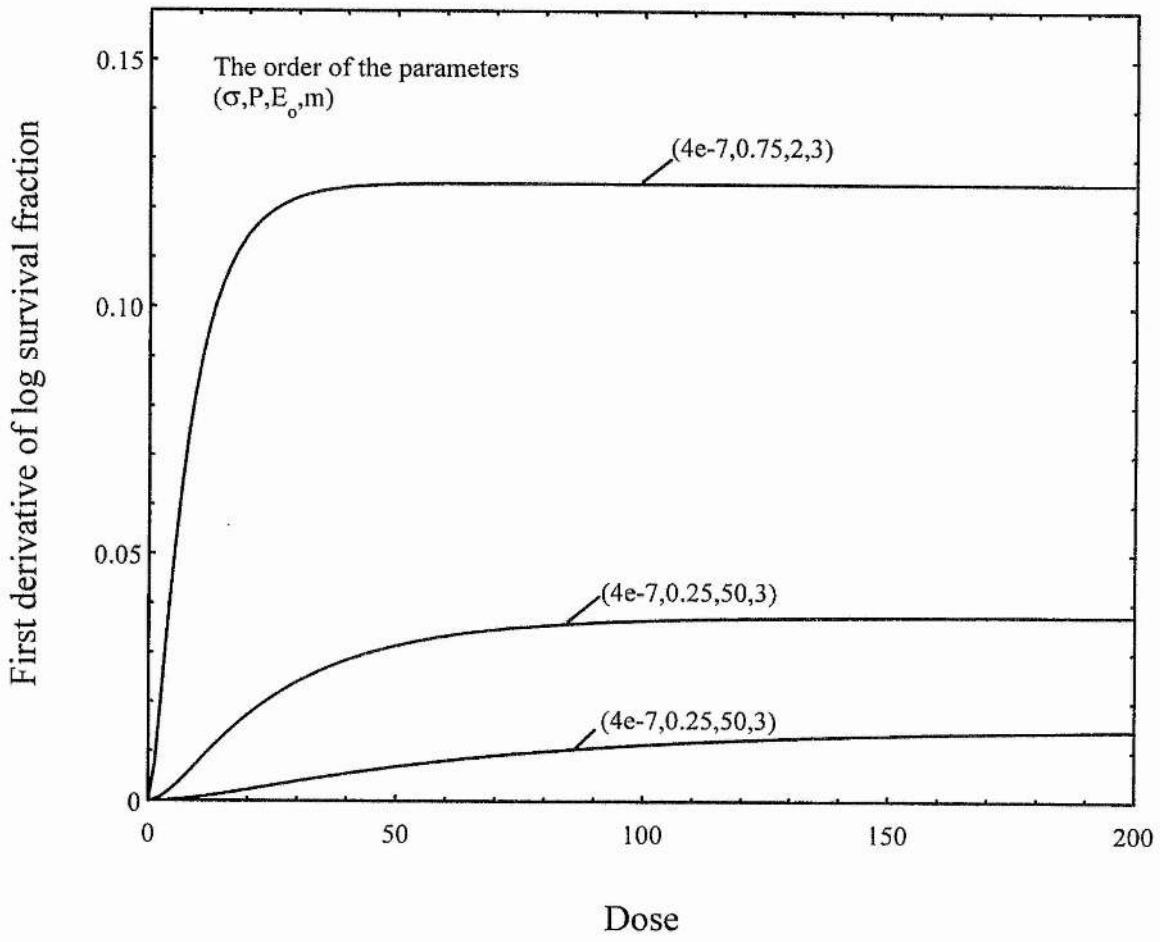


Fig. 2.11(b): CTS Model; First Derivative Log Survival Fraction (SF) against Dose, D

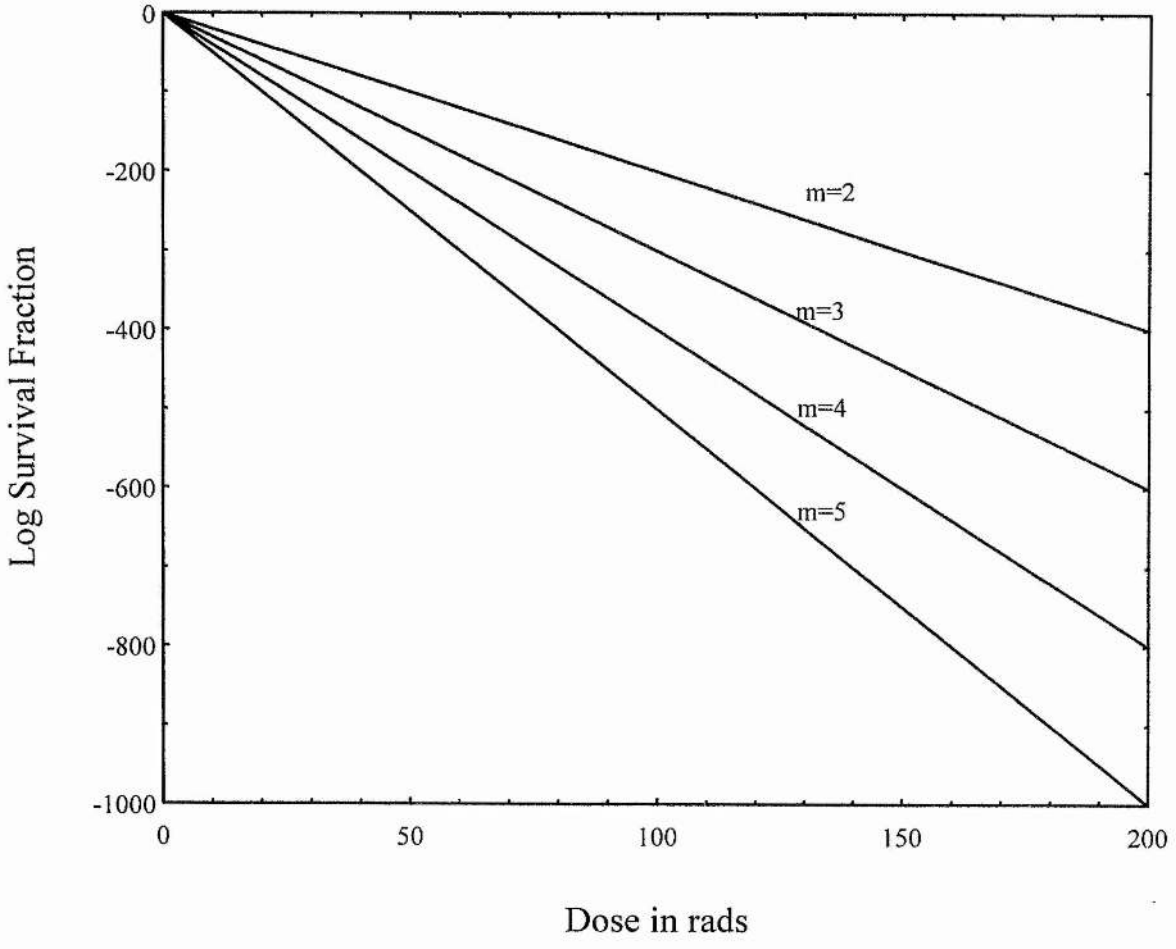


Fig. 2.12(a): HSE Model (Bond and Varma); Log Survival Fraction (SF) against Dose, D

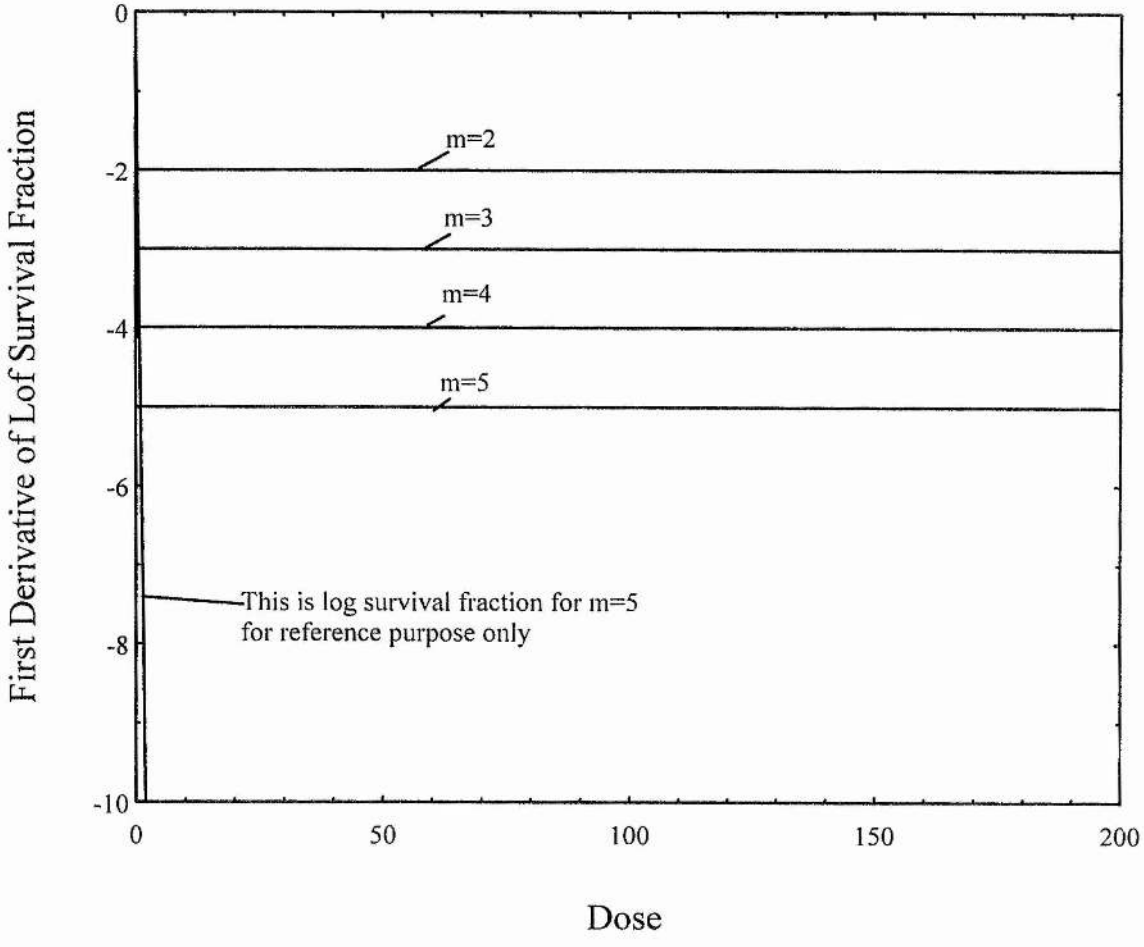


Fig. 2.12(b): HSE Model; First Derivative Log Survival Fraction (SF) against Dose, D

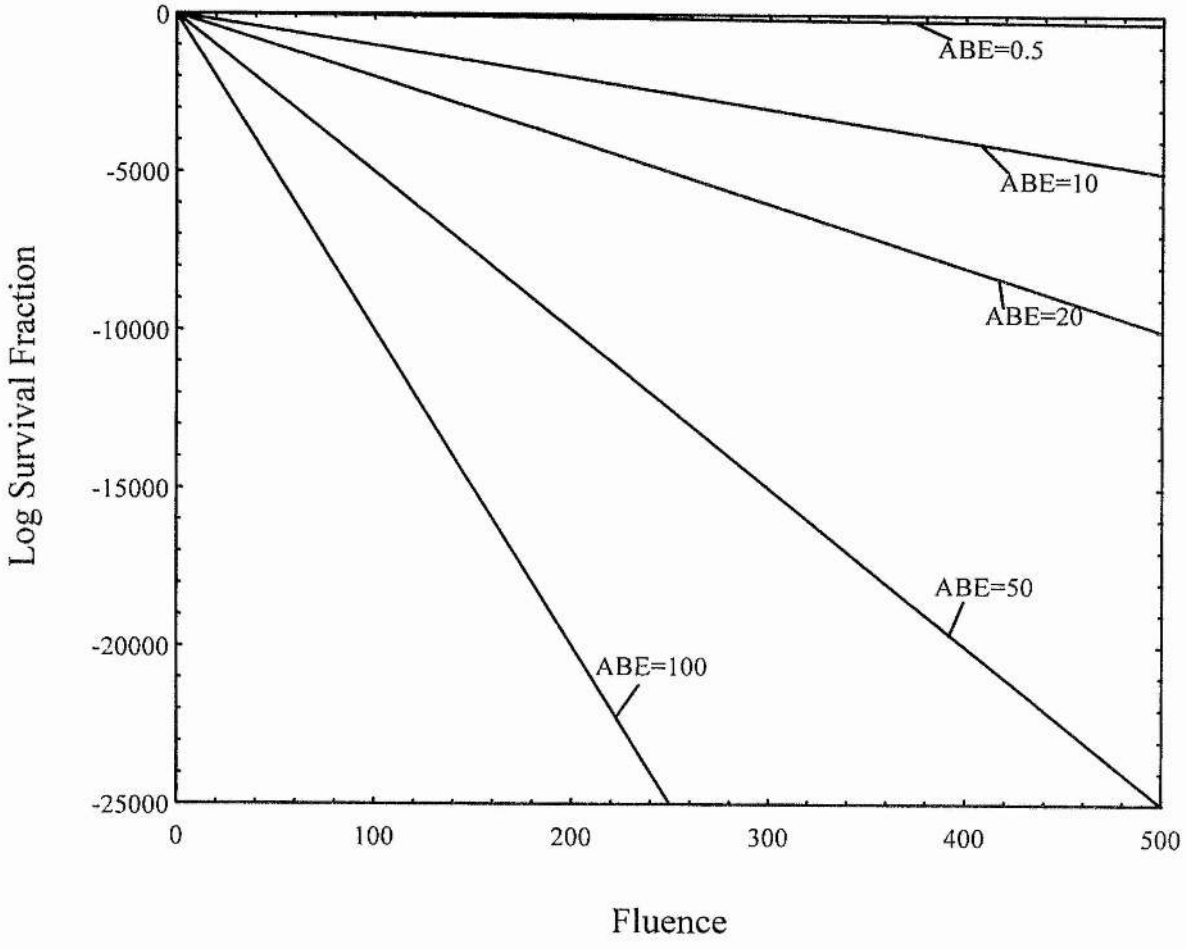


Fig. 2.13(a): TC Model (Watt); Log Survival Fraction (SF) against Fluence, ϕ

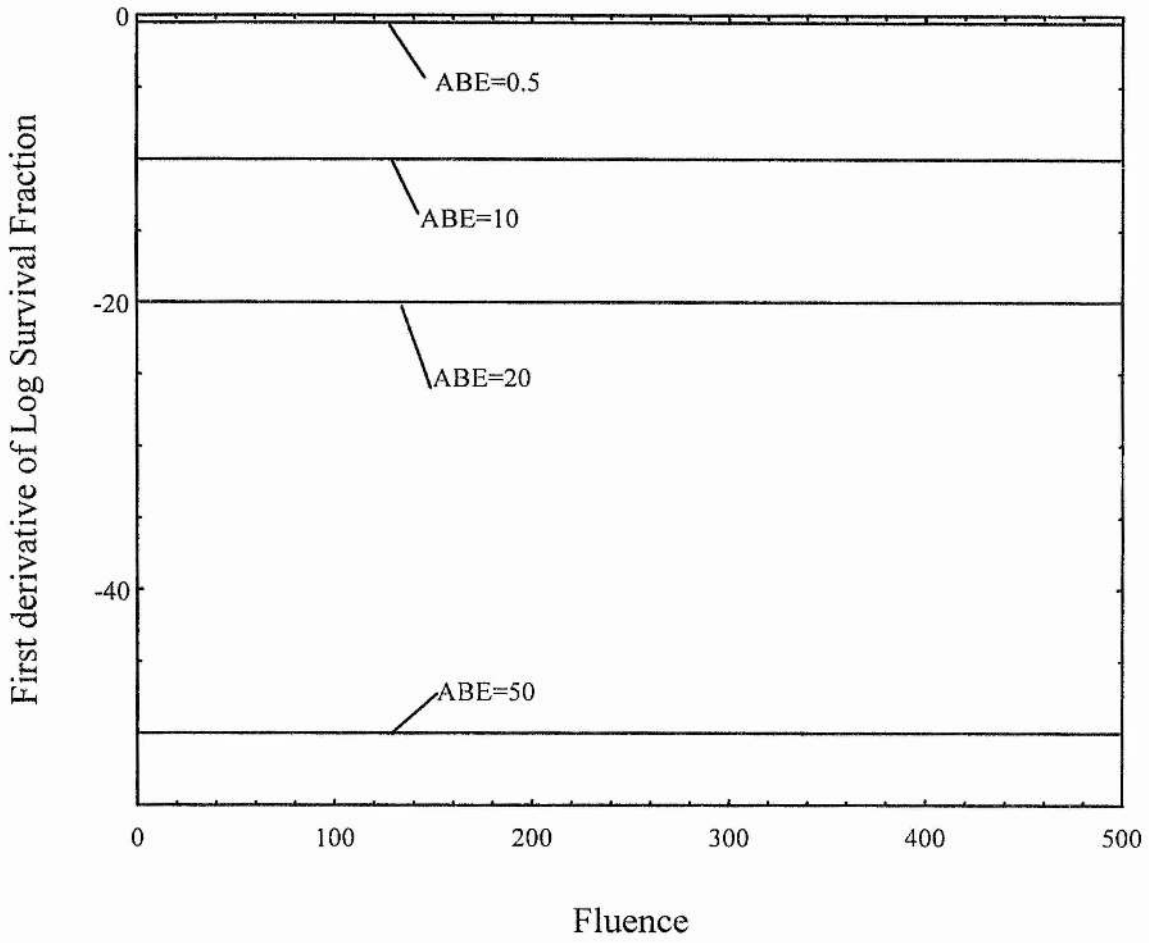


Fig. 2.13(b): TC Model; First Derivative Log Survival Fraction (SF) against Fluence, ϕ

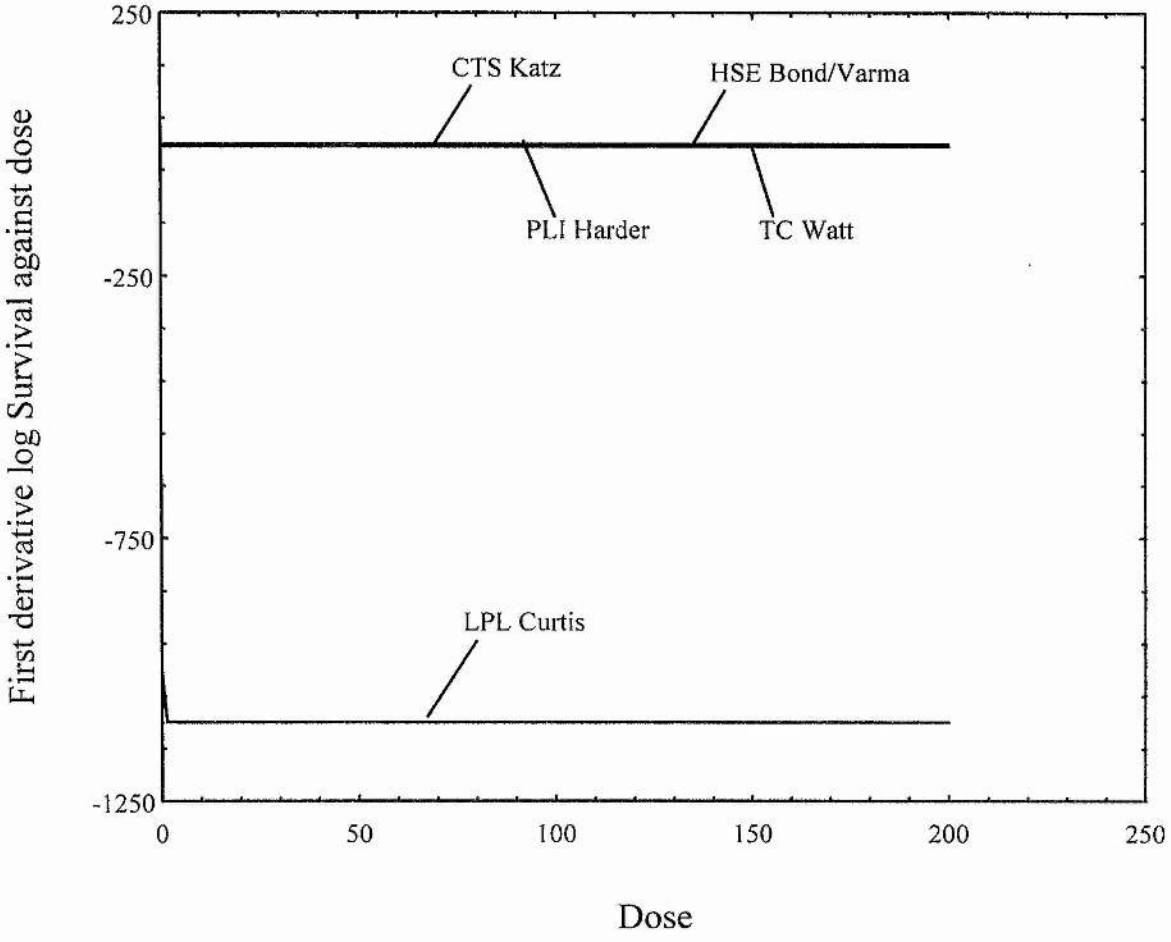


Fig. 2.14: The Overall Graphical Illustration for all models; First Derivative against Dose, D

Table 2.5: Parameters used for the overall graphical illustration for all models

Models	Parameters values	Remarks
LPL model by Curtis	η_L=1000, η_{PL}=100, ε_{PL}=20, ε_{2PL}=10, t_r=500, η=10, ε=2	
PLI model by Harder	n=5, D_q=200	The curve shows slight deviation compared with the other model but has the same general trend. The deviation is lessen if appropriate values of the parameters are chosen in the display.
CTS model by Katz	L=100, σ=4e-7, P=0.25, E_o=20, m=3	
HSE model by Bond and Varma	m=4	
TC model by Watt	ABE=50, L=100	The model for γ and neutron will differ due to the range R of the charged particles generated (see page 84).

2.6.2. Intercomparison Based on Experimental Data.

Three sets of experimental data [121] are used for this purpose. The general characteristics of the data sets are:

i. Set 1: data which indicate that there is an initial slope and final slope (table 2.6);

ii. Set 2: data which indicate that it is a continuously changing with the amount of radiation (table 2.7); and

iii. Set 3: data which is purely exponential in nature (table 2.8).

In this exercise the equation which corresponds to each of the models is used to curve fit the data. The results are shown in figures 1(a,b,c), 2(a,b,c), 3(a,b,c), 4(a,b,c) and 5(a,b,c). The overall qualitative result of this exercise is shown in table 2.9.

Table 2.6: Survival Data with an Initial Slope and Final Slope Characteristics

No	Dose x (Gy)	Survival Fraction
1	0	1.0
2	1.0	6.0E-1
3	2.0	2.5E-1
4	2.9	1.0E-1
5	4.0	5.0E-2
6	5.0	1.4E-2
7	6.0	5.6E-3

Table 2.7: Survival Data with Continuously Changing Survival Fraction

No	Dose x (Gy)	Survival Fraction
1	0	1.0
2	1	7.0E-1
3	2	5.2E-1
4	4	2.0E-1
5	6	6.0E-2
6	8	1.8E-2
7	10	2.4E-3

Table 2.8: Survival Data with Purely Exponential Survival Fraction

No	Dose x (Gy)	Survival Fraction
1	0	1.0
2	0.5	3.5E-1
3	0.9	1.2E-1
4	2.0	1.6E-2
5	2.9	2.8E-3
6	4.0	4.2E-4

Fig. 1a: Curtis Model with Data Set 1

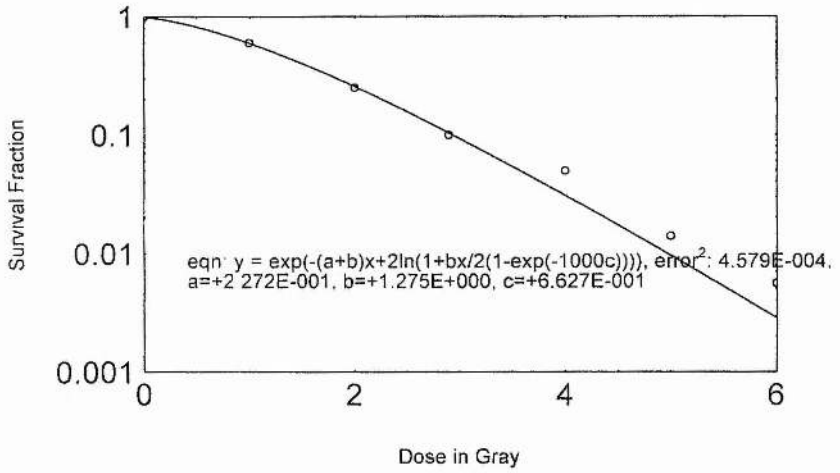


Fig. 1b: Curtis Model with Data Set 2

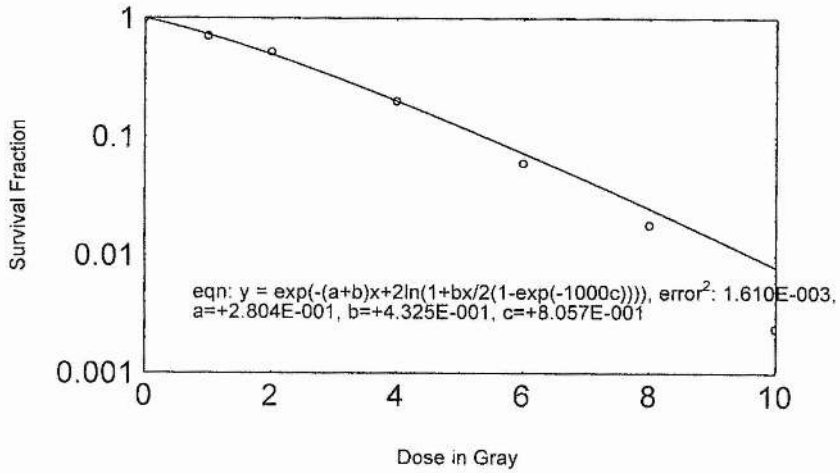


Fig. 1c: Curtis Model with Data Set 3

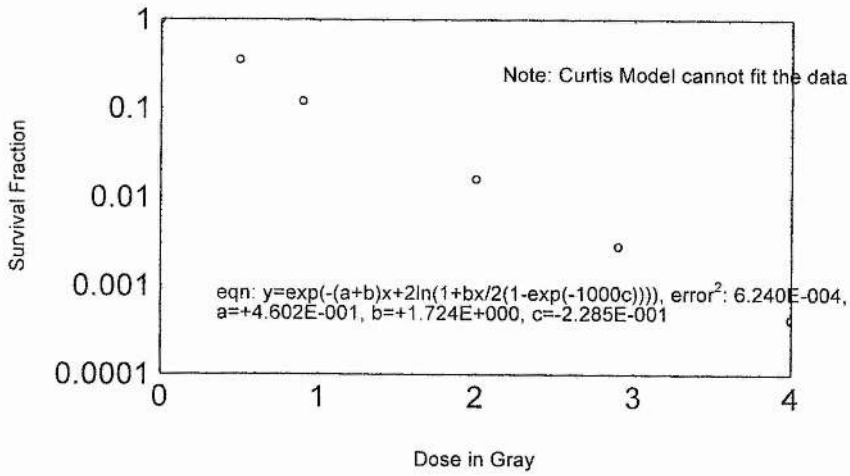


Fig. 2.15: Curtis Model based on experimental data

Fig. 2a:Harder Model using data set 1.

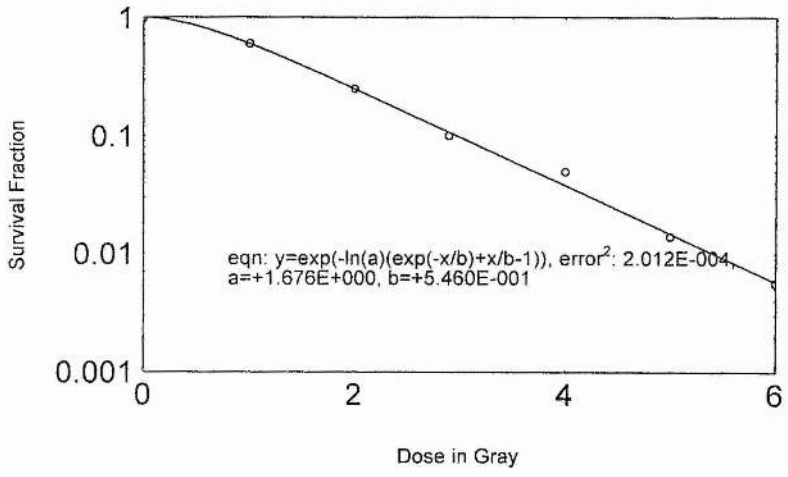


Fig. 2b: Harder Model with Data Set 2

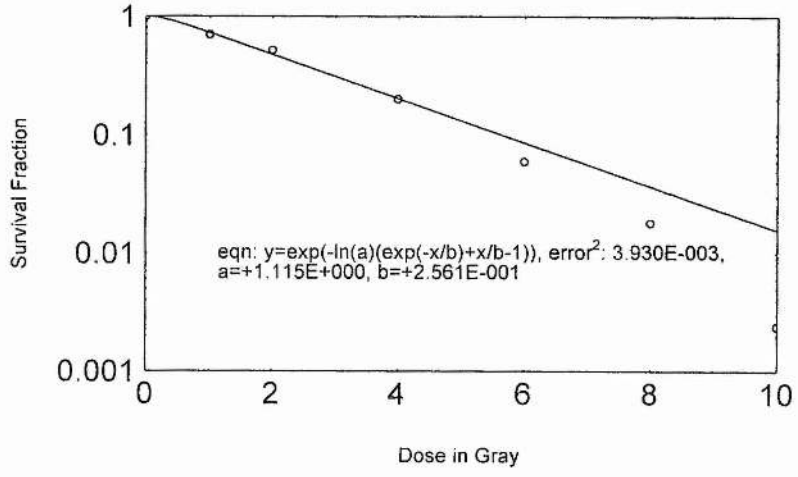


Fig. 2c: Harder Model with Data Set 3.

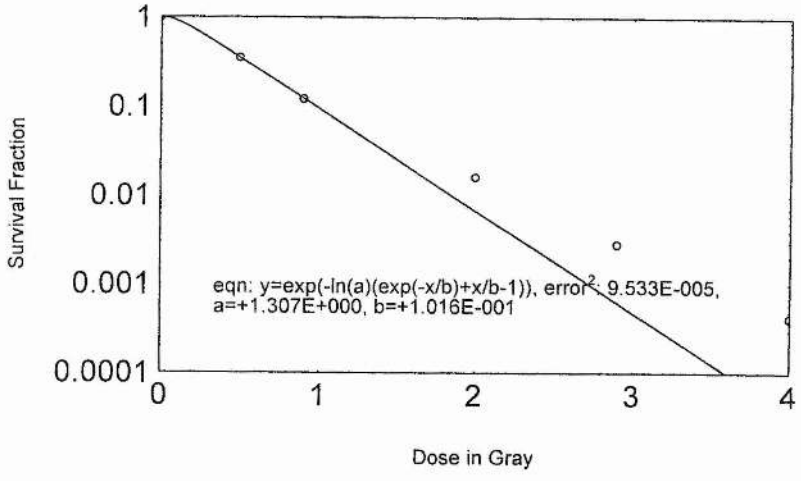


Fig. 2.16: Harder Model based on experimental data

Fig. 3a: Katz Model with Data Set 1

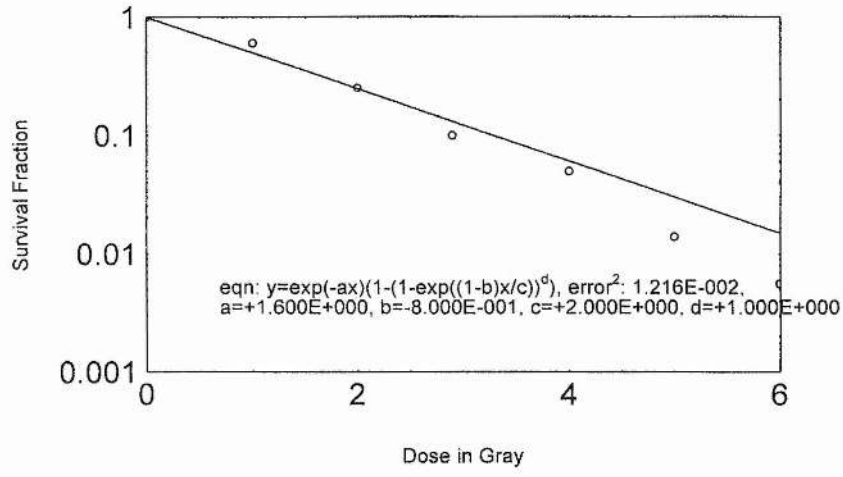


Fig. 3b: Katz Model with Data Set 2

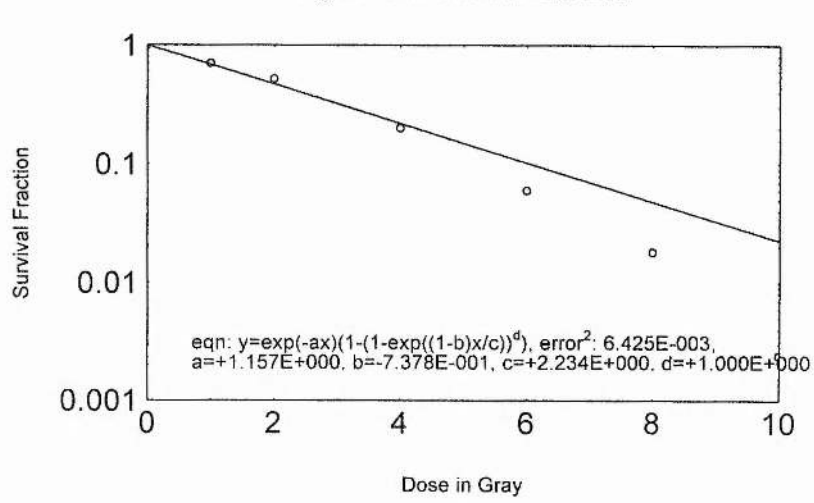


Fig. 3c: Katz Model with Data Set 3

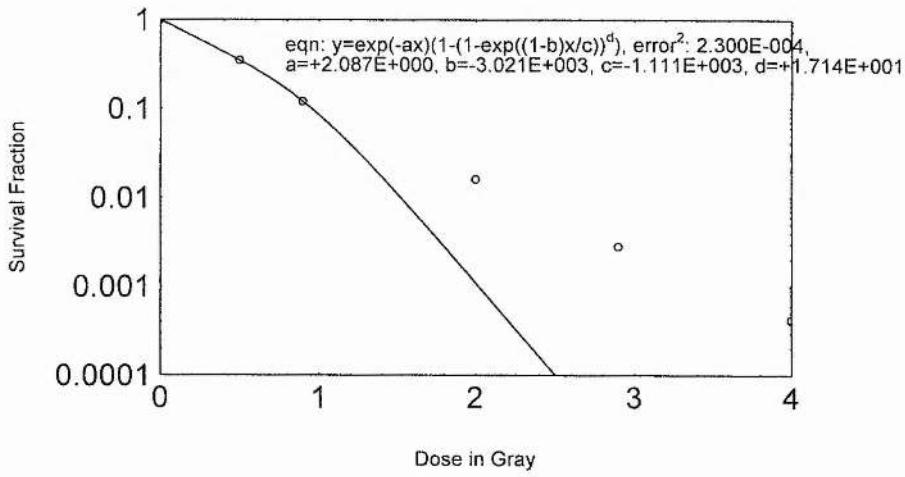


Fig. 2.17: Katz Model based on experimental data

Fig 4a: Bond and Varma Model with Data Set 1

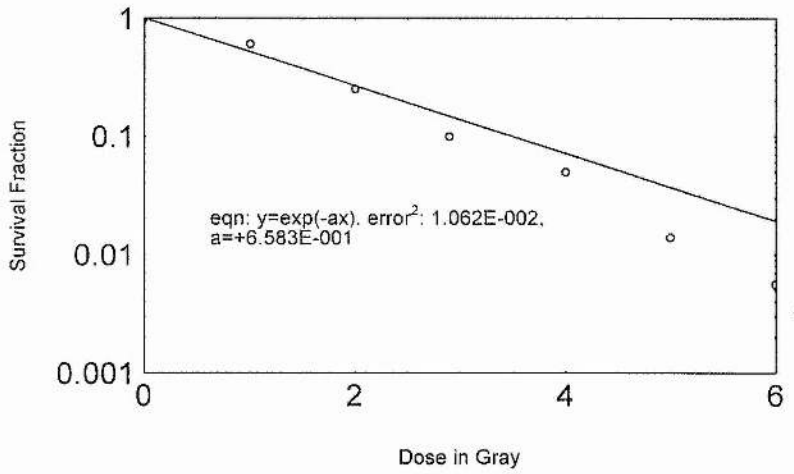


Fig. 4b: Bond and Varma Model with Data Set 2

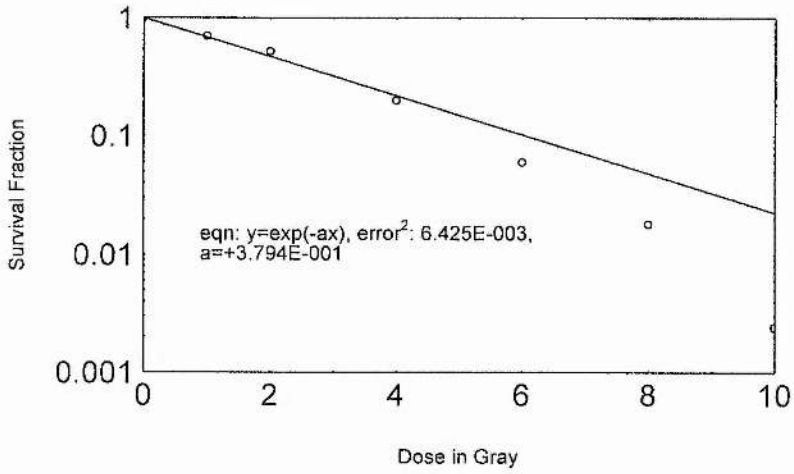


Fig. 4c: Bond an dVarma with Data Set 3

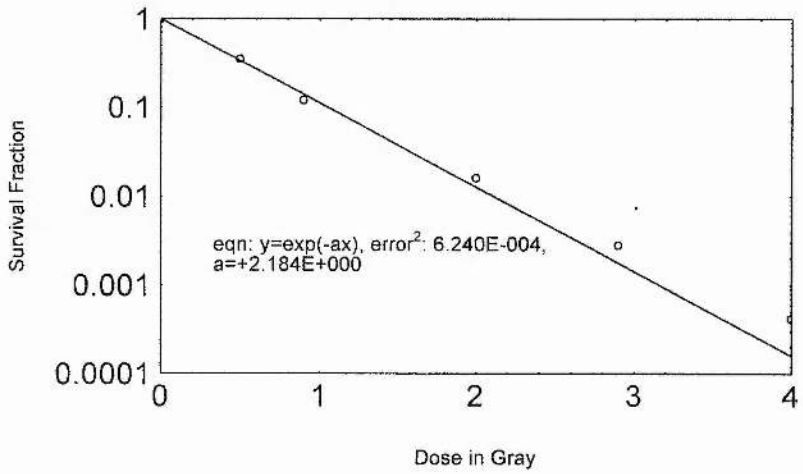


Fig. 2.18: Bond & Varma Model based on experimental data

Fig. 5a: Watt Model with Data Set 1

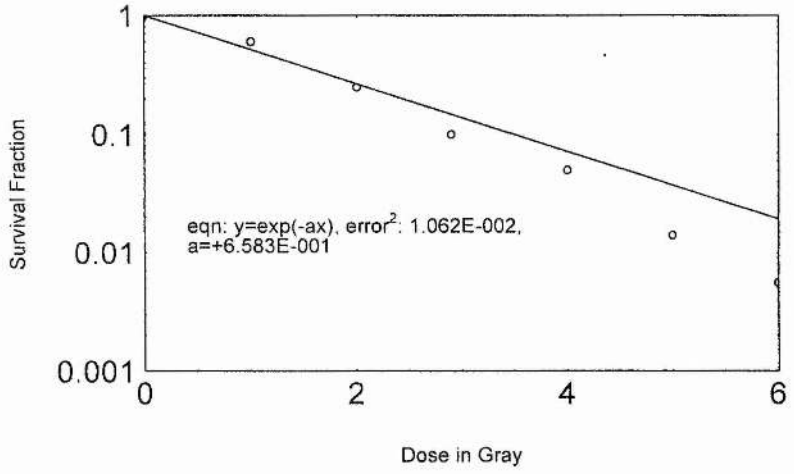


Fig. 5b: Watt Model with Data Set 2

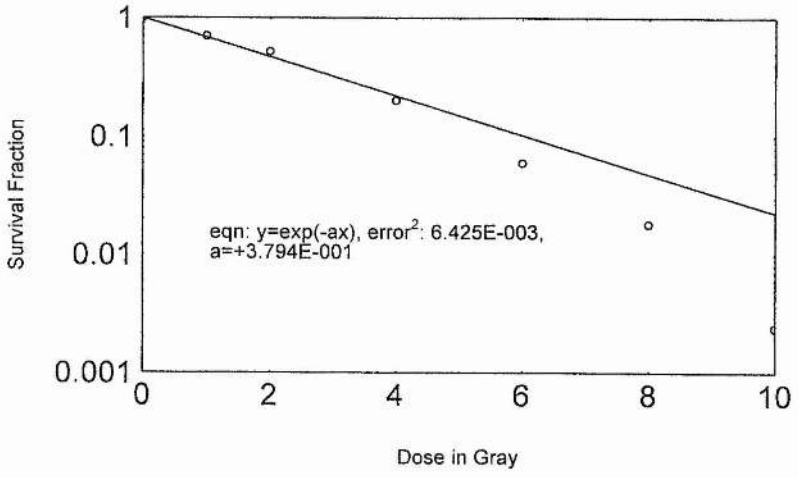


Fig. 5c: Watt Model with Data Set 3

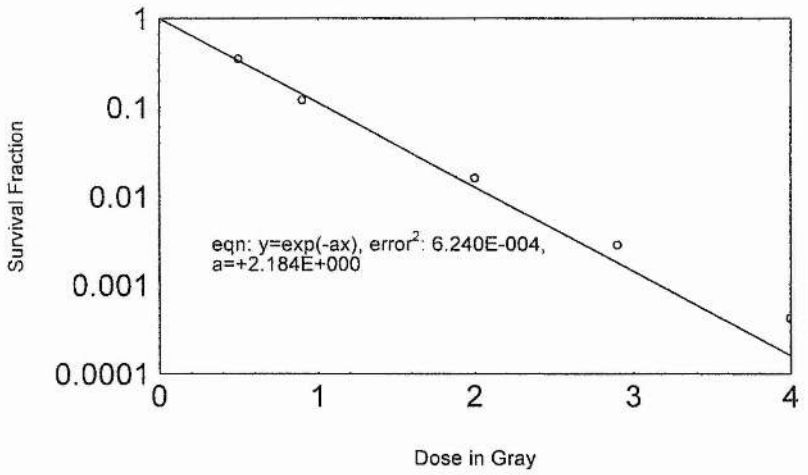


Fig. 2.19: Watt Model based on experimental data

Table 2.9: Overall Qualitative Model Intercomparison Based on the Experimental Data Sets

	Model	Curtis	Harder	Katz	Bond & Varma	Watt
1	Initial slope	Yes	Yes	Yes	Yes	Yes
2	Final Slope	No	No	No	No	No
3	Values of the Parameters	Yes (i.e. within range)	Yes	Yes	Yes	Yes
4	Basis of the model	Dose	$L_{100,D}$	Dose	Hit Size (microdo-simetry)	λ

Note:

Yes indicates that the model is responsive to the criteria; and
No indicates that the model is not responsive to the criteria.

2.6.3. Overall Conclusions

The ability of a particular biophysical model to predict the response of a particular end-point, cannot be judged only by its ability to curve fit the experimental data. For an empirical biophysical model, i.e. one which employs sets of empirical data in its development, the uncertainty in predicting the response is further increased, if the model is used to extrapolate the response in the range outside of the empirical data used. The uncertainty may somewhat be reduced if the model is used to predict the response by interpolation.

Among the problems of using an empirical biophysical model are:

i. Most biophysical models can fit any reasonable experimental data by adopting a suitable set of values for the parameters used in the model;

ii. Most empirical models are suitable for interpolative purposes. Often other possible equations may be used to interpolate the data points in a specified range. However it is less defensible if the model is used to extrapolate data outside the range of the empirical data used.

In radiological protection one of the main objectives of a biophysical model is to predict the response at lower doses, by using the model to extrapolate response from high doses to lower doses. It is believed that a biophysical model which is developed based on only empirical data, is not complete and suitable for the radiological protection purpose. A practical and realistic model must be conceptually sound and the basis used in the development of the model can be justified and supported by theoretical as well as practical knowledge of the underlying mechanisms. This type of model is then suitable to be used to predict the response by extrapolation from high doses to lower doses. This concludes that the basis of the model and the meaning of the parameters supported by current knowledge, theoretically and practically, are more important. However the chosen model must also show to some extent that it is capable to fit the empirical data.

Based on the arguments presented in this section, among the five main biophysical models of radiation action appraised and intercompared, Track Core (TC) model is chosen due to the following points of merit:

i. fluence is a superior parameter to quantify the radiation (which is believed to be better than dose). Indeed radiation effect depends on the number of particle tracks which actually pass and activate with certain probability (cross section), the sensitive sites of the system i.e. DNA double strand;

ii. ABE is used to quantify the cross section of the effect i.e. response, which is relatable to the induction of DNA dsb which is believed to be the precursor to cellular inactivation, mutation and neoplastic transformation; and

iii. The model derived is based on experimental observation and well supported theoretically.

Validity of any biophysical model of radiation action could be further tested by not only external radiation but also internal irradiation from incorporated radionuclides. It should be able to explain unusual phenomena, such as the reverse dose-rate-effect for transformations [122] and high inactivation probabilities of internal auger electron cascades.

In this exercise five main biophysical models have been evaluated, appraised and inter-compared. To proceed with this work, the TC model by Watt has been chosen. This model has been derived directly from experimental data (see section 2.4.5.9). It can offer an interpretation of the auger electron cascades of internally incorporated radionuclides and predicted the reverse dose rate effect. The basis used in the model, is used to investigate an alternate dosimetry system for radiological protection (see chapter four).

CHAPTER THREE
CANCER RISK COEFFICIENTS FOR RADIOLOGICAL PROTECTION

3.1. General

Cancer risk has received utmost consideration in radiological protection mainly because it is likely to be the only significant stochastic effect for individuals exposed to ionizing radiation [123]. How can one ensure that all reasonable steps are taken to reduce the induction of stochastic effects which is in compliance with the present system of dose limitation? Two stochastic effects which have been identified are cancer and hereditary effects. Stochastic effects can be reduced in frequency by lowering the dose but cannot be avoided entirely because there is still a finite probability of occurrence with low frequency, at lower doses. The risk of these effects has to be reduced to a value, not exceeding the risk in other safe industries. Cancer induction by radiation which has become the primary effect of concern at low doses, is given more emphasis due to the current progress achieved on the subject and due to the accumulation of recent data from the epidemiological as well as laboratory studies relevant to cancer. A prudent judgement has to be made by the various national authorities responsible for radiological protection, to incorporate the appropriate level of risk, in the legal system of radiological protection.

ICRP has incorporated the most recent cancer risk coefficients for radiological protection purposes, in ICRP Report no. 60 [34], which is discussed under the probability of cancer induction. There are two projections of risk models, which can be used to derive the cancer risk coefficients. The projected risk models are termed the absolute (risk) or additive projection model; and the relative (risk) or multiplicative projection model.

The dosimetry system currently applied in radiological protection uses dose and the relative biological effectiveness (RBE) as the basis of the system. Dose is defined as the amount of energy imparted in a unit of mass of the irradiated material. The RBE is used to indicate the relative effectiveness of a particular type of radiation with respect to x-rays or γ-rays for a specified biological end-point. Quality factors

(Q) and radiation weighting factors (w_R) are allocated safety factors based on a study of RBE and used in operational radiological protection to take care of various radiation qualities in order to derive the dose equivalent and equivalent dose respectively. The meaning of the quantities and terms commonly used in the system will be given in brief in this chapter.

3.1.1. Cancer Induction by Radiation

Ionizing radiation has been identified as a carcinogenic agent [124][125]. The exact mechanism of cancer induction by radiation and other agents, has not been firmly established yet but evidence is mounting to indicate that it is a multi-step process [126]. The general concept of the origin of cancer is that of "an event or events in one or more cellular mechanisms leading to autonomous cell division and finally expressed as complete or partial cellular escape from local or general control by the surveillance system, homoral or cell mediated" [127]. There may be many different initial events to initiate the series of changes which result in malignancy. However the transformed cells may be neutralized by spontaneous reversion or repair by excretion or by various control mechanisms or such processes as differentiation or cell death. The development of a cancer is believed to occur in multiple changes and to proceed in sequential stages. At least three processes are involved in the cancer induction namely initiation, promotion and progression. The initial events in the genome and the production of a cell or cells with the potential to develop into a cancer are known as initiation. In the promotion process the initiated cells must undergo further changes, after stimulation by a promoting substance to become a cell with malignant potential. Sometimes the promoted cell is called a **precancerous cell**. Progression is the stage where the division and multiplication of the promoted cell (i.e. precancerous cell) gives rise to an occult tumour.

The carcinogenic process, includes the growth of a primary cancer to a detectable size, about 1 cm in diameter with billions of cells. Changes in the genome i.e. total chromosome content of a germ cell, may take place in the germinal cells of the reproductive tissue, which may be manifest as hereditary disorders in succeeding generations. Modifications in a single cell such as neoplastic transformation leading

to malignancy, may have serious consequences. Death of one or a small number of cells, in most cases, have no consequences in tissue. Alterations in normal cells caused by ionising radiation, can give rise to cancer occurrence. The probability of such a change is proportional to dose, at very low doses. On average less than one event per sensitive target in a cell occurs. For example, 1 mGy of 1 MeV gamma rays, result on average 1 (or occasionally more than 2) tracks per cell nucleus; and 1 mGy of 1 MeV neutrons, result about 10^{-2} tracks per cell nucleus. In a DNA molecule, there are about $2x10^9$ of 2 nm segments. Assuming the contribution of δ-rays is negligible, the probability of energy being deposited in a particular 2 nm segment is small, in the order of 10^{-9} per track.

Initial event may involve more than one step in which radiation interaction is not necessarily the first. A clone of cells with malignant potential may arise and eventually a cancer may develop. The probability of cancer induction is far lower than that of the initial events, because of host defence and the failure of succeeding changes required by the initiated cells.

3.1.1.1. Latency Period

On the average the latency period for all cancers is 10 years. The shortest latency period is for acute myeloid leukaemia which is equal to 2 years [34].

3.1.1.2. Generalization of cancer induction by radiation

For high LET, low dose rate or fractionation, may have;

a. similar effect to that of high dose rate single exposure in some cancers; or

b. others, more effective than high dose rate, single exposure.

Certain chemicals can increase the rate of tumour induction by synergistic effects, for example 12-o-tetradecanoyl phorbol-13 acetate and asbestos. However some chemicals can decrease the rate of tumour induction such as Vitamin A analogue. For a given organ or tissue the risk of cancer induction is assumed proportional to the number of irradiated cells at risk.

3.1.1.3. For low LET (cancer induction)

There is little direct data available for low dose low LET cancer induction. Exposures are often at high dose rates. Therefore in order to establish a dose response relationship the following are taken into consideration:

i. theoretical considerations; and

ii. experimental data and limited human exposure (Japanese survivors from atomic bomb attacks. 1945).

Initiation of cancer is associated with the induction of lesions in genomic DNA that result in specific gene loses and/ or changes in gene structure. However the DNA repair system which involves an enzyme system, is able to recognise and remove lesions from the DNA. The repair system is apparently more effective after low dose rate exposure than that of high dose rate exposures, which will introduce the dose and dose rate effectiveness factor (DDREF) between high and low dose rates. The general conclusions by the NCRP (1980) on the dose-response relationship are as follows:

i. for high doses, at high dose rate rates, the relationship is likely to be linear-quadratic in form; and

ii. for low doses at low dose rate, the relationship is expected to be linear at low doses.

NCRP defines the dose rate effectiveness factor (DREF) as the ratio between the slope of the linear no-threshold fit to high dose , and the slope of the linear no-threshold fit to low dose data. NCRP also assumes that the value of DREF varies between 2 and 10, whereas UNSCEAR 88 recommends DDREF values between 2 and 10. UNSCEAR 93 recommends DDREF values about 2 and may not be more than 3.

3.1.1.4. Dose and Dose Rate Effectiveness Factor (DDREF) for low LET

Cancer induction at low doses and low dose rates should be less than observed after high dose and dose rates. The ICRP recommends for radiation protection purposes, to use the value of DDREF equal to 2 [34].

3.1.1.5. Cancer induction after exposure to high LET radiation

Penetrating and short range high LET radiations are more damaging than low LET

radiations per unit absorbed dose. For cell killing RBE values are about 2 or 3 and rise as the doses decrease. For deterministic effects RBE values do not exceed 10. For stochastic effects the RBE of high LET is a function of dose determined by the shape of the dose response relationship. The maximum value, i.e. RBE_m (a constant value), at low doses where both the low LET and high LET dose-response curves become linear. Figure 3.1 shows that for high LET, fractionation is more effective than for low LET. **Reverse dose-rate effect** is the **increase** of the effectiveness with decreasing dose rate and or fractionation (in some cases for high LET radiation) at low doses.

3.1.1.6. Estimates of Probability for Carcinogenic Effects

New information on the risk of radiation induced cancer has emerged from human populations and from experimental data in both laboratory animals and cultured cells, which include the following:

i. About 90,000 survivors of the atomic bombs in Japan, are continually assessed, initially by using the official Tentative Dosimetry System 1985 (T65D) and recently 76,000 of them are assessed by using Dosimetry System 1986 (DS86). The estimates of the probability of cancer death from 1950 - 1985 are increased over earlier estimates because of:

   a. The increase in the number of cases (excess solid cancer) about 135 in 1975, and about 260 in 1985: Leukaemia, about 70 in 1950-1975, and about 80 in 1950-1985;

   b. The new dosimetry system (DS86), apparently increases the probability values by about 30 percent only. However according to Thiessen et-al [128] there are two more important factors related to the increase namely:

      i. There are indications that those who were exposed while very young are now beginning to demonstrate an increased risk of radiogenic cancer; and

      ii. The relative risk projection model is better to represent the atomic bomb survivors data than the constant absolute risk projection model;

   c. Small changes in methods used to calculate the age specific

probability of cancer: and

d. Preference for the multiplicative model rather than the additive model for projection of the solid cancers to lifetime values (section 3.3);

ii. Solid cancer data from about 14,106 patients suffering ankylosing spondylitis followed up after undergoing radiotherapy treatment.

The main basis for ionizing radiation risk estimate is the data from the atomic bomb survivors. The bombs were dropped in Hiroshima and Nagasaki on the sixth of August and the ninth of August 1945, respectively. A list of the total number of malignancies in the survivor population by site of cancer as well as an estimate of the excess number of malignancies by site for all dose categories, all ages at exposure and both sexes, is shown in table 3.1. Other data are also available as reported in the literature which includes accidental exposures, occupational exposures (mining, dial painters), medical therapeutic (ankylosing spondylitis) and diagnostic exposures.

From the molecular biology point of view, radiation can inactivate oncogenes which will be expressed somatically to produce malignant tumours. An oncogene [129] is a particular type of gene in the DNA which, if affected by radiation (e.g dsb), will lead to malignancy. The first oncogene discovered was **src gene** which can induce tumours in chickens [131] and over 25 additional oncogenes have subsequently been discovered.

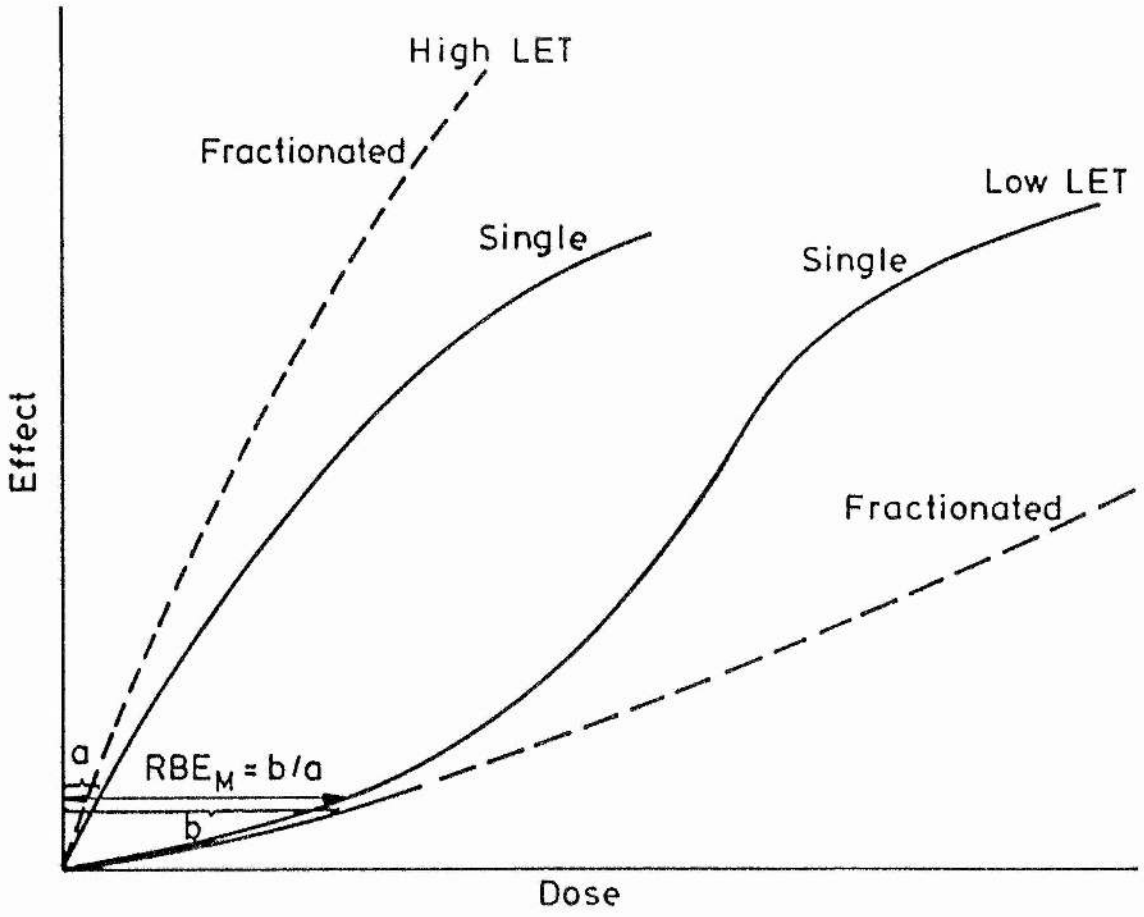


Fig. 3.1: Shapes of dose responses for low LET and high LET radiations plotted on linear axes (Sinclair 1982)

Table 3.1: Atomic Bomb Survivor Data for the Period of 1950 to 1985.

Site of cancer	Total cancer cases[a]	Number of excess cancer cases[b,c]
Leukaemia	202	78
All cancer except leukaemia	5,734	266
Oesophagus	176	11
Stomach	2,007	72
Colon	232	19
Lung	638	44
Female breast	155	22
Ovary	82	10
Urinary tract	133	19
Multiple myeloma	36	8
Remainder	2,275	61
Total for all sites	5,936	344

[a] Data from Shimizu et-al. (1988).
[b] Assumes an average shielded kerma of 0.162 Gy.
[c] The number of cases are for all exposure categories up to and including the 4+ Gy category.

3.1.2. Risk Assessment

Radiation risk assessments have been carried out by various competent national as well as international authorities, dealing with radiological protection. In the following sections of the chapter the risk assessment carried out by the ICRP will be presented in brief. However the induction of cancer is given more emphasis than the other effects due to current progress and the availability of recent data in this field. Epidemiological study on the survivors of the atomic bombs in Japan, population of more than 90,000, is the most important single source of information for estimating the relationship between cancer risk and radiation dose.

Lambert [130] has noted that a full assessment of radiation risk at low levels have to include genetic and somatic effects. However the carcinogenic effect (somatic) is considered more important because cancer are often lethal and cancer is the only statistically verifiable cause of life shortening at low and intermediate doses. Its assessment at occupational or environmental doses (i.e. mSv per year or a few tens of mSv) is difficult by direct observation. Only the epidemiological studies such as on the Japanese survivors of the atomic bombs, will likely resolve uncertainties in our estimates of cancer risk.

One of the developments in risk assessment is to take the quality of life into consideration. Dennis [131] has pointed out that the input from social scientists may add other weighting factors in radiological protection which reflect the public evaluation of the hazards from different sources. For examples why, in the public view is a sievert from the discharges of nuclear power processing plant not the same as the sievert from radon at home or from medical diagnosis? In the public view also there are fates that may be worse than death such as permanent paralysis below the neck or protracted terminal cancer.

3.2. Cancer Risk Coefficients

3.2.1. Cancer Risk Assessment by ICRP

3.2.1.1. Introduction

ICRP has clarified the term **risk** and decided to abandon its practice of always strictly using **'risk'** with the specific meaning of 'probability' and to attempt to use, where practicable, the more direct term **probability**. Risk is a concept rather than

a quantity. It may be seen as a multi-attribute quantity. Therefore according to ICRP, **risk assessment** is not necessarily synonymous with **probability assessment** but may include assessment of other aspects of risk: the nature and severity of the harmful consequences.

The Commission is concerned with two quantifiable risk quantities, namely:

i. The probability of each harmful effect (i), P_i

The effect will have to be specified eg. lethal cancer or curable cancer, severe hereditary harm, etc.; and

ii. The consequence if the effect occurs, w_i

The consequence can be described in a variety of ways, indicating the severity of the effect and its distribution in time.

The mathematical expectation of consequence, identical to the average consequence, is given by:

$$\overline{W} = \sum_i P_i \, w_i$$

when averaging is relevant, where;

P_i the probability of each harmful effect (i); and

w_i the consequence if the effect occurs.

It is a quantity which is sometimes used in the effort to express the magnitude of the risk by one single measure. In the individual case, the mathematical expectation (W=P.w) is not an **expected** result, because the only possible outcomes are zero or w measure of harm.

Example:

Given that, the probability of losing, on average 20 years of life because of cancer, is equal to 10^{-6} (i.e. $P=10^{-6}$). The expectation of loss of life i.e. W=P.w, is equal to 10^{-6}x20 years $=2x10^{-5}$ years (i.e. about 10 minutes). The real loss of life is either zero with probability P, equal to $P=(1-10^{-6})$ or about 20 years with probability equal to $P=10^{-6}$.

So the use of the expectation, in this case masks the fact that it is composed of the two components P and w. The probability of death is the major factor in the multi-attribute concept of risk. Other attributes should also be considered, such as illness, hereditary disease, risk to any fetus, economic losses, anxiety and other societal impacts.

The dose limits recommended in the ICRP publication 26 [35], were put forward with the implied assumption that an annual occupational death probability of about 10^{-3} to the most exposed individuals would be at the border of being unacceptable. The corresponding death probability for members of the public at the annual limit of 1 mSv would be about 10^{-5}.

3.2.1.2. The Risk of Death

Radiation induced cancers are indistinguishable from cancers induced by other agents. Radiation risk has been expressed as **the percentage probability of death per Sievert**. The introduction of a new risk source will only change the distribution of the probable causes of death, but will not change the lifetime probability of death. The total probability of death is 100% and it can not be increased. The introduction of a new risk source will only change the distribution of the probable causes of death. So, any increment that a new risk source causes, is an increment to the death probability rate at any given age, provided that the person is alive at that age (i.e. conditional probability rate).

The total conditional death probability rate from all causes can usually be described by the Gompertz-Makeham expression:

$$G_o(U) = A\, e^{BU} + C$$

where

$G_o(U)$ is the total conditional death probability rate from all causes, for an average person given that the individual is alive at every age U;

U is the age in years; and

A,B,C are parameters derived from demographic tables.

A constant dose rate from age 18 to 65, may add a conditional source related increment of probability rate, dP/dU, to the background rate:

$$G(U) = G_0(U) + \frac{dP}{dU}$$

where,

G(U) is the total conditional death probability rate from all causes including radiation, for an average person;

$G_0(U)$ is the background rate; and

dP/dU is the conditional source related increment of probability rate.

3.2.1.3. The Background Conditional Death Probability Rate [$G_0(U)$]

$G_0(U)$ (excluding radiation) according to Gompert-Makeham is given by the following expression:

$$G_0(U) = A\, e^{B.U} + C.$$

Usually $G_0(U)$, the lowest when U=10 years and the annual probability of death is about 1-2 in 10,000 in industrialised countries and 1 in 1,000 in developing countries. For choosing a dose limit, it is necessary to examine the overall risk picture and the Commission prefers a multi-attribute approach to the choice of dose limits.

3.2.1.4. Primary Risk Coefficients K_{D,A_0} and C_{D,A_0}

A radiation dose, if received by an individual at a given age, will involve a risk commitment, namely a commitment of an increased cancer death probability rate in the future, after a minimum latent period for specific types of cancer. The occurrence of cancer requires a minimum latent period of time elapsed since the radiation exposure. The risk committed by a radiation dose at a given age therefore cannot be added to the background risk at the same age. An increased cancer death probability rate (dp/du) will occur only after a minimum latent period of time since the radiation exposure. In the case of internal exposure, the committed effective dose may be delivered to a specified organ long after the intake of the radioactive substance, which further delays the expression of harm. Two models have been used for risk projection with time:

i. Additive or absolute model

The excess probability rate is dose dependent but age independent; and

ii. Multiplicative or relative model

The excess rate increases with age at the same rate as the background cancer rate.

3.2.1.5. Methodology: Models for Projection of Probabilities

Two principle models for the estimation of probability of cancer induction have been used viz. the absolute (risk), or additive projection model; and the relative (risk), or multiplicative projection model. The absolute or additive model predicts, after a minimum latency period, the constant excess of induced cancer throughout life unrelated to the spontaneous rate of cancer. The relative or multiplicative model predicts, after a minimum latency period, the excess of induced cancer will increase with time as a constant multiple of the spontaneous or natural rate of cancer, and consequently will increase with age in that population.

The total death rate (per year at age a) $q_{D,A_o}(a)$ is given by:

$$q_{D,A_o}(a)=q_o(a) + h_{D,A_o}(a)$$

where

$q_o(a)$ is due to natural causes; and

$h_{D,A_o}(a)$ is the excess death rate due to dose D at age A_o.

The probability of surviving $L_{D,A_o}(a)$ until age a after a given dose D at age A_o is:

$L_{D,A_o}(a)=1$ for $a \leq Ao$; and

$L_{D,A_o}(a)=L_{D,A_o}(a-1).\{1-q_{D,A_o}(a-1)\}$ for a=Ao+1, ...

where

$L_{D,A_o}(a-1)$ is the probability of survival until age (a-1); and

$q_{D,A_o}(a-1)$ is the death rate at age (a-1).

Survival to age a implies survival to age (a-1) and precludes death at age (a-1). So the **probability of survival until age a** is the **product** of the **probability of survival until age (a-1)** and **{1- (total death rate per year at age (a-1)}**.

The annual probability of death from any cause at age a is equal to $L_{D,A_o}(a).q_{D,A_o}(a)$. The annual probability of a radiation induced death at age a is equal to $L_{D,A_o}(a).h_{D,A_o}(a)$.

The lifetime probability of a death due to radiation exposure D at age Ao is equal to U(Ao,D) given by:

$$U(Ao, D) = \sum_{a=Ao}^{maxage} L_{D,Ao}(a) \cdot h_{D,Ao}(a)$$

If in interval (A1, A2) where Ao ≤ A1 ≤ A2, the cumulative mortality $R_{D,Ao}$(A1,A2) is given by:

$$R_{D,Ao}(A1, A2) = \sum_{a=A1}^{A2} L_{D,Ao}(a) \cdot q_{D,Ao}(a)$$

Note that the annual probability of death from any cause at age a is equal to the product of the surviving probability to age a [$L_{D,Ao}$(a)]; and the total death rate at age a [$q_{D,Ao}$(a)]. The annual probability of death due to radiation exposure is equal to the product of the surviving probability to age a [$L_{D,Ao}$(a)] and the death rate due to cancer $h_{D,Ao}$(a).

The expression for the total death rate (per year at age a) $q_{D,Ao}$(a) is given by:

$$q_{D,Ao}(a) = q_o(a) + h_{D,Ao}(a)$$

where

q_o(a) is due to natural causes; and

$h_{D,Ao}$(a) is the excess death rate due to dose D at age A_o.

In the simple additive model:

$h_{D,Ao}(a)=0$ for $a < Ao + m$; and

$h_{D,Ao}(a)=K_{D,Ao}$ for $a \geq Ao+m$

In the simple multiplicative model:

$h_{D,Ao}(a)= 0$ for $a < Ao + m$; and

$h_{D,Ao}(a)=C_{D,Ao} \cdot q_{o,(cancer)}(a)$ for $a \geq Ao+m$

where

$K_{D,Ao}$ and $C_{D,Ao}$ depend on D and Ao, but not on a;

$q_o(a)=q_{o,(cancer)}(a)+q_{o,(non\text{-}cancer)}(a)$; and

$q_{o,(cancer)}$(a) is the component of q_o(a) that pertains to the specified cancer being considered.

Table 3.2: Primary risk coefficients for annual cancer death (UNSCEAR, 1988). These risk coefficients have been derived on the basis of observations on the cancer death rate among the survivors from the atomic bombing of Hiroshima and Nagasaki. They relate to high doses and high dose rates and are strictly applicable to the Japanese survivors only. "ERR"=excess relative risk.

Age at exposure (years) Ao	Males		Females	
	Additive $10^{-2}Sv^{-1}$ and year $K_{D,Ao}$	Multiplic. ERR/Sv $C_{D,Ao}$	Additive $10^{-2}Sv^{-1}$ and year $K_{D,Ao}$	Multiplic. ERR/Sv $C_{D,Ao}$
(a) Leukaemia				
0 - 9	0.0384	18.7	0.0300	19.5
10 - 19	0.0203	4.4	0.0104	4.6
20 - 29	0.0434	5.6	0.0249	5.8
30 - 39	0.0631	3.9	0.0196	4.1
40 +	0.0472	3.3	0.0318	3.4
(b) all cancer but leukaemia				
0 - 9	0.0148	1.06	0.0407	2.06
10 - 19	0.0526	0.65	0.0707	1.27
20 - 29	0.126	0.57	0.137	1.11
30 - 39	0.114	0.24	0.137	0.48
40 +	0.164	0.18	0.186	0.34

3.2.1.6. Convention on acceptable risks

Our daily activities, such as walking, motor-cycling, horse riding, driving etc. carry some risks. Some activities are accepted and some are not accepted even though the risks have been reduced as far as reasonably achievable. Society has accepted an unspoken convention on **risk acceptance** in order to enjoy the benefits of a modern society, provided that the risks are not unnecessary or easily avoided. But what levels of risk are acceptable?

Example:

> From a report of a study group of the British Royal Society (1983); imposing a continuing annual occupational probability of death of 1 in 100 would be unacceptable. The situation imposing an annual probability of death of 1 in 1000 is less clear, either acceptable or unacceptable. However the annual probability of death is only one attribute which is appropriate to take into account. The annual probability level of 1 death in 1000 could 'hardly be called totally unacceptable provided the individual at risk knows of the situation, judged he had some commensurable benefit as a result, and understood that everything reasonable had already been done to reduce the risk'.

3.2.1.7. Assessment Based on the Additive and Multiplicative Models

The results of assessment based on the additive and multiplicative models, carried out by the ICRP are as shown in figures 3.2, 3.3, 3.4, 3.5 and 3.6. The value of the parameters used in the assessment are as follows:

i. L= 2 years for Leukaemia;

ii. L=10 years for other cancer;

iii. P=40 years for Leukaemia;

iv. P=infinity for other cancers;

v. DDREF is assumed equal to 2;

vi. Exposure age A_o= 5 years and 35 years;

vii. The conditional death probability rate (dP/du);

viii. The unconditional death probability rate (dr/du); and

ix. The attributable lifetime probability of death (R).

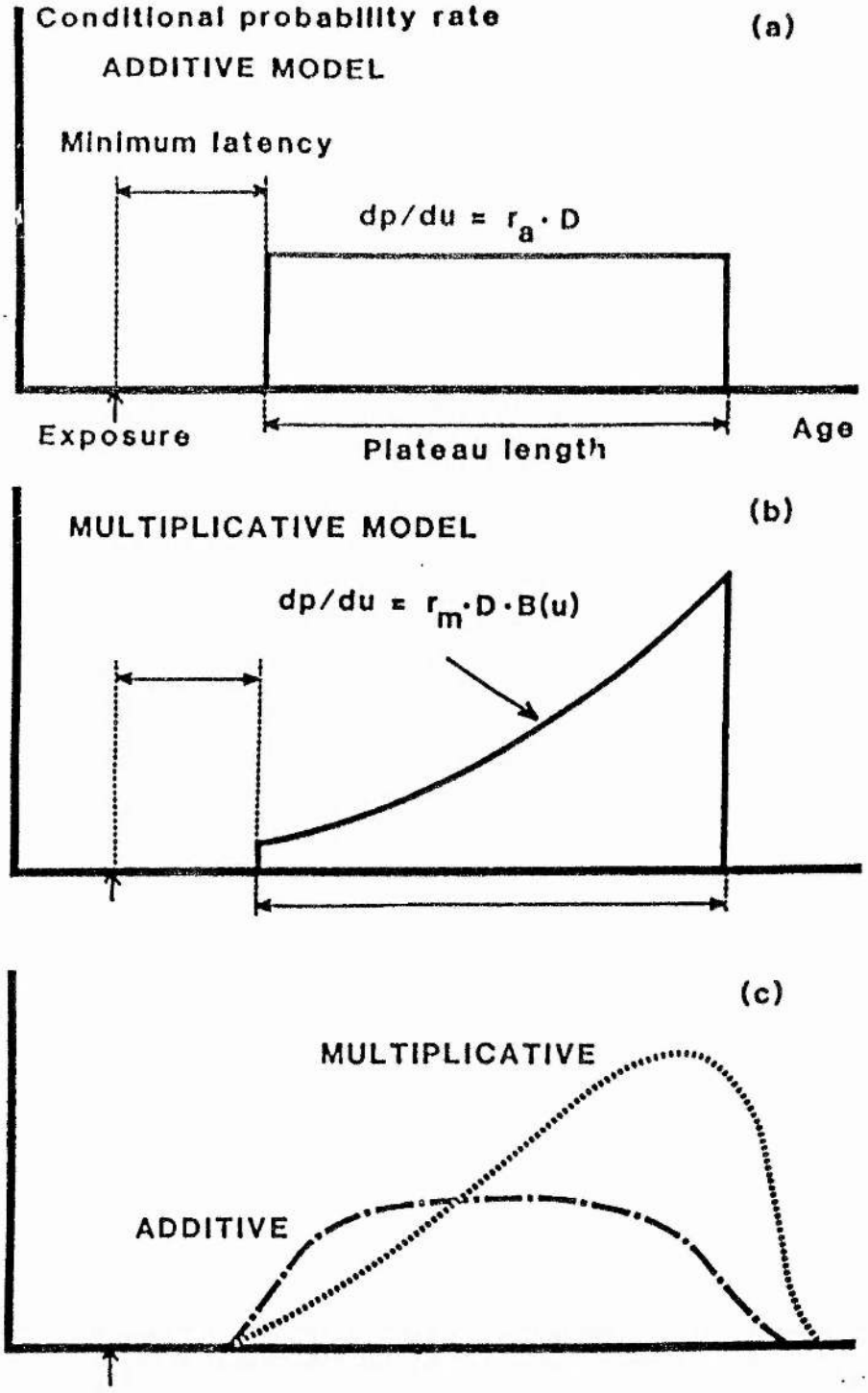


Fig. 3.2: Illustration of the two simple projection models. Figures (a) and (b) show the stylised models which have been used for the calculations; Figure (c) indicates possible curve shapes under more realistic assumptions. (a) The simple additive model: The excess conditional probability rate (of death from cancer) after a single radiation dose D,is assumed to be proportional to the dose, but first after a minimum latency period and over a plateau period of time. (b) The simple multiplicative model: The excess probability rate is also assumed to be proportional to the background rate of cancer death, B(u).

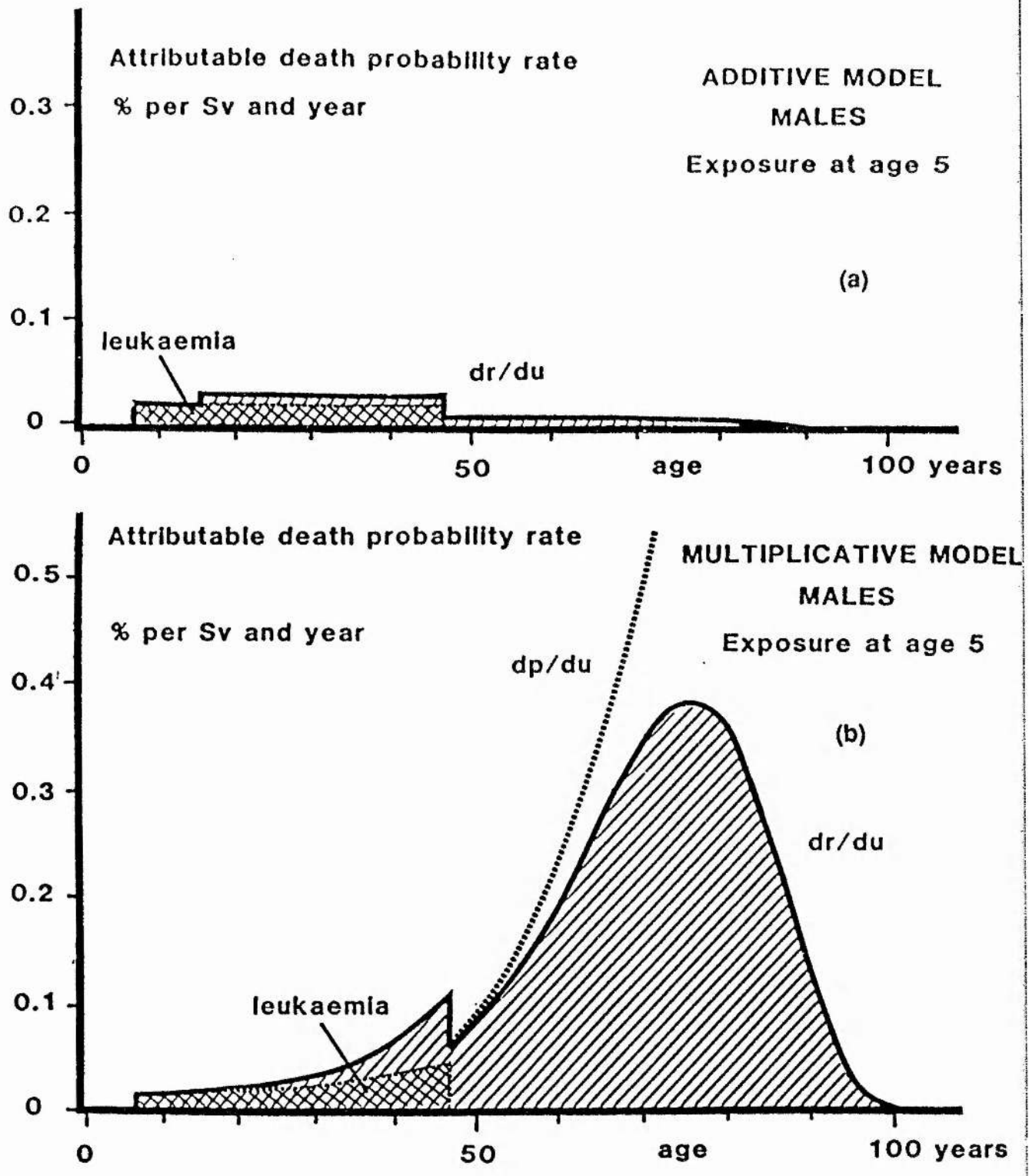


Fig. 3.3: Variation with age of the attributable death probability rate dp/du (conditional) and dr/du (unconditional) after a single small dose at age 5 years, assuming a DDREF of 2. The discontinuities reflect the simplified assumptions on minimum latency periods and plateau shapes (refer to figure 3.2)

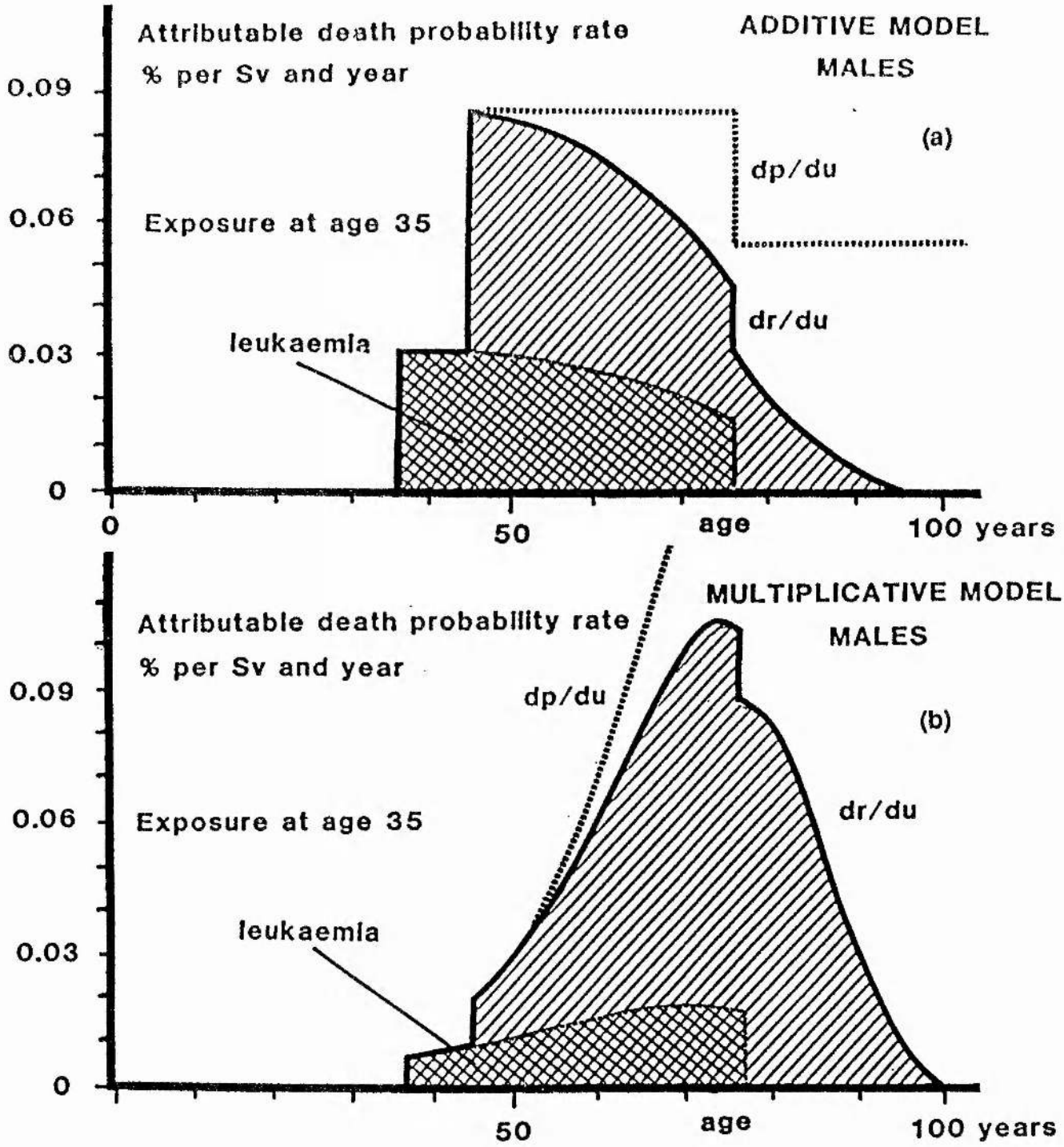


Fig. 3.4: Variation of age of the attributable death probability rates after a small single dose at age 35 years, assuming a DDREF of 2. The discontinuities reflect the simplified assumptions on minimum latency periods and plateau shapes (refer to figures 3.2 and 3.3).

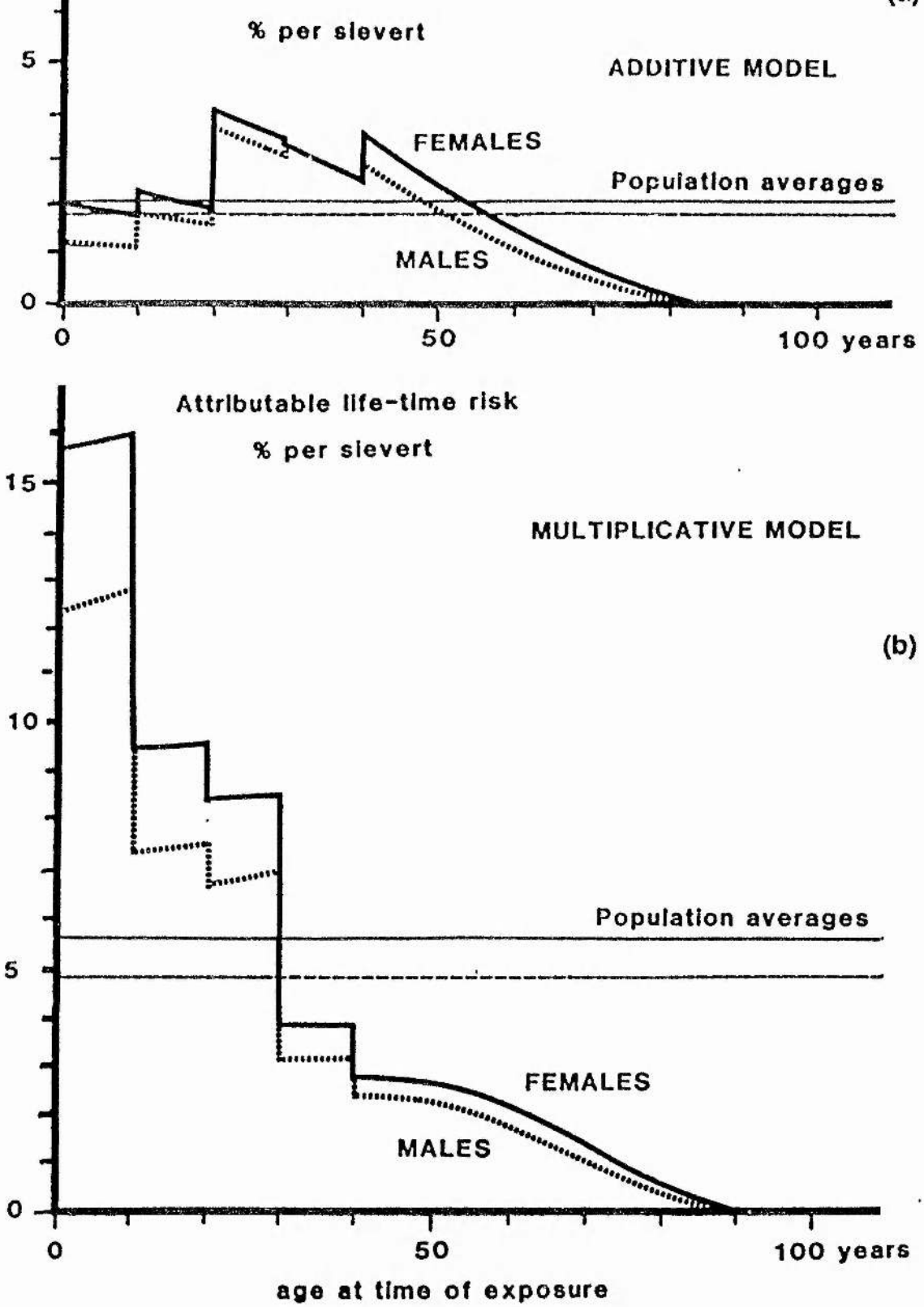


Fig. 3.5: The attributable lifetime risk from a single small dose at various ages at the time of exposure, assuming a DDREF of 2. The discontinuities are the result of the use of constant annual values for the primary risk coefficients within 10-year age interval. The higher risk for the youngest age group will not be expressed until late in life.

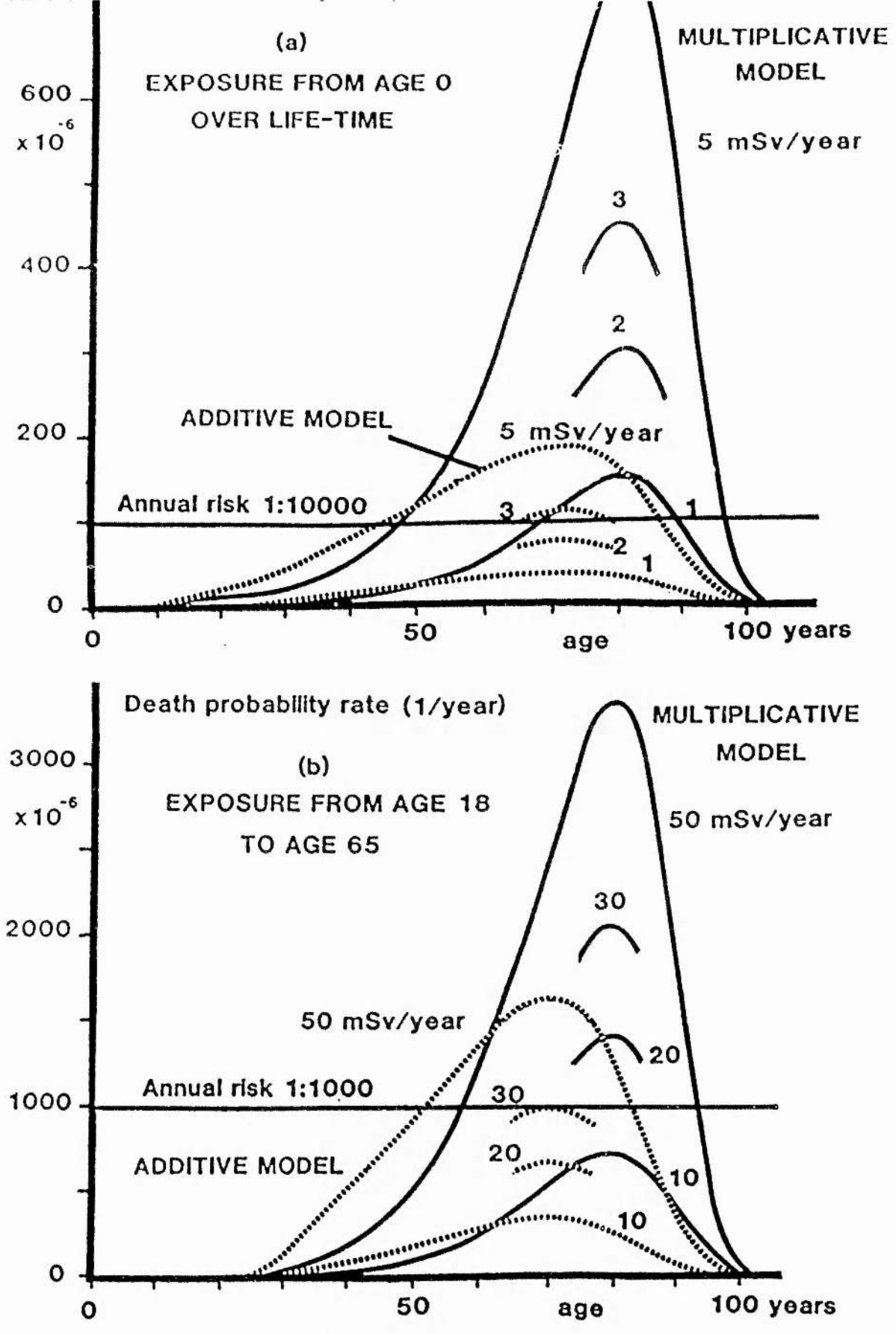


Fig. 3.6: The unconditional death probability rate (the attributable probability density of the age of death, normalised for lifetime risk) for two exposure situations: (a) exposure from birth over lifetime, and (b) exposure from age 18 to age 65 years. The curves are for females, assuming a DDREF of 2.

3.2.1.8. Conclusion

The results of the ICRP risk assessment are as follows:

i. For workers the risk which corresponds to a dose limit of 20 mSv per year is determined from the cancer risk coefficient of $4x10^{-2}$ Sv^{-1} (called the 'nominal probability coefficient' by ICRP) to be equal to $20x10^{-3}x4x10^{-2}= 8x10^{-4}$ per year; and

ii. Similarly, for the general population the dose limit is 1 mSv per year and the cancer risk coefficient is $5x10^{-2}$ Sv^{-1} which corresponds to a risk of $1x10^{-3}x5x10^{-2}= 5x10^{-5}$ per year.

The nominal probability coefficients for stochastic effects are summarised in table 3.3, and the nominal probability coefficients for individual tissues and organs, are given in table 3.4.

Table 3.3: Nominal Probability Coefficients for Stochastic Effects

Exposed population	Detriment (10^{-2} Sv^{-1})[6]			
	Fatal Cancer[7]	Non-fatal cancer	Severe hereditary effects	Total
Adult workers	4.0	0.8	0.8	5.6
Whole population	5.0	1.0	1.3	7.3

[6] Rounded values

[7] For fatal cancer, the detriment coefficient is equal to the probability coefficient.

Table 3.4: Nominal Probability Coefficients for Individual Tissues and Organs[8]

Tissue or organ	Probability of fatal cancer (10^{-2} Sv^{-1})		Aggregated detriment (10^{-2} Sv^{-1})	
	Whole Population	Workers	Whole Population	Workers
Bladder	0.30	0.24	0.29	0.24
Bone Marrow	0.50	0.40	1.04	0.83
Bone Surface	0.05	0.04	0.07	0.06
Breast	0.20	0.16	0.36	0.29
Colon	0.85	0.68	1.03	0.82
Liver	0.15	0.12	0.16	0.13
Lung	0.85	0.68	0.80	0.64
Oesophagus	0.30	0.24	0.24	0.19
Ovary	0.10	0.08	0.15	0.12
Skin	0.02	0.02	0.04	0.03
Stomach	1.10	0.88	1.00	0.80
Thyroid	0.08	0.06	0.15	0.12
Remainder	0.50	0.40	0.59	0.47
Total	5.00	4.00	5.92	4.74
Probability of severe hereditary disorders				
Gonads	1.00	0.6	1.33	0.80
Grand total (rounded)			7.3	5.6

[8] The values relate to a population of equal numbers of both sexes and a wide range of ages.

CHAPTER FOUR

PROPOSED NEW SYSTEM FOR RADIOLOGICAL PROTECTION

4.1. General

The proposed new system of dosimetry is called a **unified dosimetry system** which is a system for the direct assessment of the absolute biological effectiveness of ionising radiation without the need to know the radiation intensity and type, therefore, it obviates the need for quality factors. From published data on damage to yeast, plant and mammalian cells, the mean free path (λ) for ionisation of the charged particle tracks emerges as a physical parameter which best unifies data. Damage is found to be optimum when the spacing of the ionization along the tracks in the cell nucleus matches the mean strand spacing in the DNA segments (i.e. for $\lambda \sim 2$ nm). This finding is common to the induction of mutations, chromosome aberrations and inactivation [132]. Bryant [133] has indicated that the inter-strand distance between ends of a double strand break is 1.8061 nm. The damage mechanism depends on the number of interactions via the interaction cross section, and not on the amount of energy transferred (i.e. not on dose, LET, RBE etc.). In the unified dosimetry system, the mean free path for ionisation λ, of the charged particle is used as an important physical parameter of the radiation. For fast particles λ is directly proportional to z^2/β^2 and most particles are maximum damaging at energies below λ equal to ~2 nm. The parameter z^2/β^2, is proportional to the yield of delta rays per unit distance and also to the yield of primary ionization per unit distance, along a fast ion track. Absolute Biological Effectiveness (ABE) is determined as the quantity which indicates the effectiveness of the radiation at inducing DNA dsb as it penetrates through a cell nucleus. It is desirable that radiation quality be defined absolutely in terms of appropriate physical and biological parameters so that the fundamental requirements for designing radiation measuring devices can be identified. In proposing the unified dosimetry system both physical and biological parameters are taken into consideration.

The charged particle tracks are attributable to the incident fluence, whether it is of directly or indirectly ionising radiations. Radiations such as x-rays, γ-rays or low energy electrons, produce a slowing down spectrum of secondary electrons with

different energy and spatial distribution. In the unified dosimetry system, the following parameters are used:

- λ The mean free path for primary ionisation;
- ϕ_c The fluence of the charged particles at equilibrium (or the charged particle fluence);
- σ_e The effect (or action) cross section which is used to indicate the induction of a specified biological end-point per unit fluence; and
- P The damage probability or intrinsic efficiency, defined as the quotient of the effect cross section (σ_e) by the projected cross sectional area (σ_g) of the radiosensitive target i.e. $P= \sigma_e/\sigma_g$.

In conventional dosimetry quality and quantity of radiation are required to assess the biological effectiveness of a particular radiation. 'Quality' is usually expressed as relative biological effectiveness (RBE), in radiobiology or as quality factor (Q), in radiological protection whereas 'quantity' is usually expressed as absorbed dose, D. Instrumentation for measurement of radiation is designed in such a way that the response of the device which is a function of particle energy, is related to specified biological effect, as a function of energy. For example a BF_3 proportional counter can be fitted with a hydrogenous moderator to produce a long counter in which the count rate is proportional to neutron fluence rate independent of energy. In the unified dosimetry system, the signal from suitable instruments is related to the probability that exposure to the radiation field will induce cancer within a person's lifetime [134].

4.1.1. Effect Cross-section (σ_e)

The effect (or action) cross-section (σ_e) measures the probability that the effect will occur in the target per incident track per unit area. The basic definition is 'probability per unit fluence'. Hence for cell survival, the probability of survival (F) is equal to the survival fraction (SF) i.e. F=SF. Therefore for exponential survival $SF=\exp(-\sigma_{eff}.\phi)$, the effect cross-section (σ_e) is equal to the first derivative of F against fluence (ϕ) i.e. $\sigma=dF/d\phi$. For $F=\exp(-\sigma(\phi).\phi)$ with σ a function of ϕ, $\ln F=-\sigma(\phi).\phi$, therefore $\sigma(\phi)= -\ln F/\phi$. In general, for exponential survival with cross

section a function of fluence; $\sigma_e(\phi) = -\frac{d\ln F}{d\phi}$

At 37 % survival lnF=-1. therefore $\sigma \rightarrow 1/\phi_{37}$ or $1/\phi_o$ but note that the survival curve may not be a straight line on a ln-linear plot. RBE of radiation type 1 (LET track average $\bar{L}_{T,1}$) with respect to the reference radiation type 2 (LET track average $\bar{L}_{T,2}$) is given by:

$$RBE_{1,2} = \frac{D_2}{D_1} = \frac{\sigma_1}{\sigma_2} \cdot \frac{\bar{L}_{T,2}}{\bar{L}_{T,1}}$$

with an assumption that the response can be expressed as a pure exponential.

The expression for the integral fluence, ϕ_s, generated by the field radiation, takes different forms, according to whether the initial radiation field is directly or indirectly ionising and whether the experiments are performed in a track segment arrangement or under charged particle equilibrium conditions [135]. In case of:

i. External irradiation by charged particle beams in track-segment experiments;

$$\phi_s = \phi_i$$

where ϕ_i is the fluence of charged particles incident on the whole sample;

ii. External irradiation in photon or neutron beams under charged particle equilibrium conditions;

$$\phi_s = \phi_v \cdot \mu \cdot \phi_i$$

where ϕ_v is the equilibrium fluence of charged particles generated per interaction per unit volume. $\mu.\phi_i$ is the source density i.e. the product of the interaction coefficient for the indirectly ionising radiation in the medium (macroscopic interaction cross section or inverse interaction mean free path) and the incident fluence of photons or neutrons; and

iii. Internal irradiations by alpha, beta, or gamma emitters homogenously distributed in the target medium;

$$\phi_s = \phi_v .C \; ; \; \phi_v = R_p . F_s$$

where ϕ_v is the equilibrium fluence of charged particles generated per unit

source strength and C is the concentration of source activity in the sample. R_p is the range of the frequency weighted average energy of primary charged particles representing the decay spectrum emitted by the source activity of concentration C. F_s is the build-up ratio of secondary to primary charged particle fluence.

The degree of damage is determined predominantly by the number and correlation of physical interactions and not necessarily by the amount of energy transfer. The cross-section for radiation effect σ_e for the incident charged particles, is used to quantify the degree of biological damage. Radiation effect is expressed in terms of the quantity 'intrinsic efficiency of action', P, for the charged particle track which actually enters a well defined geometric cross-section area σ_g of the irradiated specimen [136]. Thus $P=\sigma_e/\sigma_g$ where σ_g is the whole molecule in the case of enzymes, the cross-sectional area within the protein coat for viruses, or the cross-sectional area of the nucleus for cells. Most recent work indicates that σ_g could be best defined as the geometrically projected cross-sectional area of the nuclear DNA.

4.1.2. Calculation of Effect Cross Section (σ_e)

By assuming that cellular material has density ρ, the microscopic cross-section for induction of the effect by individual charged particle radiations (effect cross section σ_e) can be extracted from the dose survival curves, by the following formula;

$$\sigma_e = 1.6 \times 10^{-9} \frac{\bar{L}_T}{D \cdot \rho} cm^2$$

where

$\bar{L}_T$ is the track average LET in kev.μm^{-1} for the relevant charged particle energy spectrum;

D is dose in gray; and with an assumption that it is a pure exponential response; and

ρ is the density taken as unity in gcm^{-3}.

For fast charged particles (accelerated ions) in track segment experiments, L is calculated for the primary ion tracks and D is taken as the dose which corresponds to 37% survival fraction. For X and γ irradiation, the effect is due to the slowing

down recoil electron spectrum in transient equilibrium. $\bar{L}$ refers to the track average LET for the spectrum and D corresponds to the D_0 quoted by the original authors. or averaging the slope over the approximately linear portion of the survival curve [137].

The foregoing biophysical interpretation of the mechanism of radiation effects are to be applied to the currently accepted system of dosimetry for radiological protection. The method of risk assessment applied to the Japanese bomb survival data, will be reinterpreted within the new model (section 4.4.1).

4.2. Deduction of St. Andrews' Model

The approach used for developing a model of radiation action in the University is first to correlate on a single curve the information reported on cellular effects observed in a variety of irradiation circumstances, for many radiation types and for a variety of biological end-points. Attempt has been made to quantify the observed survival data as effect per unit fluence of track, in the relevant charged particle spectrum. For photons and neutrons, the respective equilibrium fluence spectra are of recoil electrons and protons. For track segment irradiation, the fluence of incident particles has been taken as equal to the equilibrium fluence spectrum. The results are expressed as a ratio to the observed saturation effect cross section to yield the effect probability (P) per incident track [137] i.e

$$P = \frac{\sigma_{effect\ cross\ section}\,(\sigma_e)}{\sigma_{saturation\ effect\ cross\ section}\,(\sigma_{sat})} = \frac{\sigma_e}{\sigma_g}$$

The saturation effect cross-section (σ_{sat}) is believed to be the projected area of the cellular DNA.

The advantages of this approach are several which include:

i. to improve 'the signal to noise ratio', (i.e. only a very small percentage of dose D is efficient) as the net observed biological effect is attributed on probability grounds to the single track which penetrates the sensitive sites (see section 2.4.5.2);

ii. to provide a method of correlating data for different target types to reveal their similarities and differences: and

iii. it has high interpretive value as the radiation track is used essentially as a probe to explore the structure of the sensitive site within the biological target. For example by expressing the damage probability as a function of the mean free path for selected physical interactions, information is obtained on the presence of significant sites and their critical linear dimensions.

The cross section ratio, or the intrinsic probability (P) represents the net intrinsic efficiency of action of single tracks in the relevant charged particle spectrum, to which the sensitive sites are exposed. Plots of P against the mean free path for ionization by the tracks λ, showed better correlation of data than that obtained for other parameters e.g. LET, and led to the following conclusions:

i. Structure is observed at a mean free path (λ) of between 1.5 and 2.0 nm and occurs only in targets containing DNA. The most probable damage is when $\lambda=\lambda_0=2$ nm. When λ is different from λ_0, the probability of damage of the ionisations occurring at the appropriate spacing λ is given by $\varepsilon=(1- \exp(-\lambda_0/\lambda))$;

ii. An analysis of chromosome aberrations indicates the same basic mechanism is involved but the probability of aberration is lower by a factor of four compared with cell inactivation. It suggests that one in four double strand breaks (dsb) leads to chromatid breaks or that two simultaneous dsb are required-pairwise lesions;

iii. The δ-rays must have relatively small effect as the extrinsic efficiency of a delta ray track is found to be less than 10^{-4};

iv. At the same mean free path (λ), the equilibrium electrons from irradiations by electrons, x-rays and γ-rays, are found to act with an intrinsic efficiency (P) of about one order of magnitude smaller than that for heavy particles, or

charged particle recoils from neutrons. In other words the absolute quality of an electron is about ten times smaller than the absolute quality of a heavy charged particle at the same mean free path λ. Electrons are effective at track ends where λ for ionisation is in the neighbourhood of 2 nm which corresponds to electron energy about 100 eV. However 100 eV electrons have penetration depths of a few nanometres and therefore they can never penetrate more than one DNA segment. Whereas heavy particles can have λ less than 2 nm in portions of their tracks, sustained for considerable distance, and thereby can penetrate 10 to 20 DNA segments; and

v. It is expected that electrons will have a saturation inactivation cross-section equal to the geometrical projected cross-sectional area presented to the incoming electron track by the DNA in the cell nucleus (i.e. about 4 μm^2 depending on the cell type). Heavy particles have a saturation effect cross-sectional area equal to 10 to 20 times this value, due to the overlap of segments of DNA at risk along a mean chord traversal of the cell nucleus. Therefore the saturation inactivation cross-section for heavy particles ($\lambda \leq$ 2 nm) and for neutrons is 40 to 80 μm^2, depending on the number of DNA segments at risk, which in turn, depends on the cell type and their exposure conditions. Neutrons probably cannot quite achieve the maximum cross-section because the proton ranges at optimum damage are less than the cell nuclear diameter.

Although no preliminary assumption is made about DNA, the critical lesion emerging from the model is the DNA double strand break (dsb). It is an obvious conclusion from direct experimental measurement and the new analysis. The yield of DNA double strand breaks (dsb) is derived from direct action, indirect action and mixed or combined effects of direct and indirect actions (see also page 72).

4.2.1. Direct Action

The cross section for dsb production by direct action (σ_d) is given by:

$$\sigma_d = \sigma_g . n_o . \varepsilon$$

where

σ_g is the projected geometrical area of the DNA ($\sigma_g \approx 4\ \mu m^2$);

n_o is the number of overlapping segments at risk along a mean chord through the cell nucleus: and

ε is the probability that at least a single interaction will occur in each of the two strands, each of thickness x, spaced at a mean chord distance of 2 nm.

The probable values of ε are:

i. For two ionisations occurring anywhere in the 2 nm distance i.e. $\varepsilon = 1-(1+\lambda_o/\lambda)\exp(-\lambda_o/\lambda)$; $\varepsilon \sim 0.3$;

ii. For one ionisation occurring in the first strand and the second within the next 2 nm distance i.e. $\varepsilon=[1-\exp(-x/\lambda)][1-\exp(-\lambda_o/\lambda)]$; $\varepsilon \sim 0.4$; and

iii. For non-saturating tracks, one hit in each of the two strands and nothing in between

i.e. $\varepsilon=\exp(-\lambda_o/\lambda)[1-\exp(-x/\lambda)]^2$; $\varepsilon \sim 0.16$.

The mean number of dsb in DNA induced per cell by direct action is given by:

$$N_{D,\,dsb} = \sigma_d \phi$$

where

ϕ is the integral equilibrium charged particle fluence in the cell nucleus; and

$\sigma_d = \sigma_g . n_o . \varepsilon$

4.2.2. Indirect Action

The mean number of dsb produced per cell by radical action is given by:

$$N_{I,\,dsb} = n_t .\ \sigma_{dsb} .\ \phi$$

and $\sigma_{dsb} = \sigma^2_{ssb}/\sigma_g$

where

σ_{ssb} is the production cross section of single strand breaks in DNA, the general form is given by: $\sigma_{ssb}=a_1.\exp(-a_2.C_{sc})[1-\exp(-a_3.\bar{L}_T/C_{DNA})]$

a_1 is a geometrical interaction cross section;

a_2, a_3 are constants;

C_{sc} is the intranuclear scavenging concentration;

C_{DNA} is the molecular density of single strands of DNA present in the cell nucleus; and

$\bar{L}_T$ is the track average LET for the equilibrium of the charged particles in the cell nucleus: and

n_t is the total number of DNA segments in the whole cell nucleus which differs with n_o.

4.2.3. Mixed Action

For mixed action the combined effects of indirect and direct actions on individual strands gives:

$$\sigma_{M,dsb}=2 . n_o . [1-\exp(-x/\lambda)] . \frac{\sigma_{ssb}}{\sigma_g}$$

$$N_{M.dsb}= \sigma_{M.dsb}.\Phi$$

and $N_{T.dsb}= N_{D.dsb} + N_{I.dsb} + N_{M.dsb}$

where $N_{T.dsb}$ is the total initial yield of double strand breaks in the absence of repair. produced by a single track in the cell nucleus.

The repair of indirect and direct damage is assumed to occur at the same rate with a mean repair time t_{rep}. A simple damage factor can be derived as follows:

$$K(t_i) = \frac{1}{t_1} . \int_0^{t_1} \exp[-(t_t - t)/t_{rep}]\, dt$$

The overall survival fraction (SF) is given by:

$$SF=\exp[-N_{T.dsb}.K(t_i)].$$

The total yield of dsb can be expressed in terms of absolute biological effectiveness (ABE) and the incident fluence ϕ and the overall survival fraction is given by:

$$SF=\exp(-ABE.\phi).$$

4.3. Revised Dosimetry System

4.3.1. Conceptual and Principles

The foundations of the unified system of dosimetry are as follows [138]:

i. The absolute specification of radiation quality is based on the probability of induction of a specified end-point (e.g. inactivation or mutation) by single charged particle tracks which actually enter the biological target. The relevant charged particles are those in the equilibrium charged particle spectrum generated in the medium by indirectly or directly ionising radiation (see page 142). The probabilities for induction of the specified damage represents the intrinsic efficiencies of action which are absolute measures of the radiation quality. The absolute biological effectiveness (ABE) can be defined in terms of the product of the geometrical cross-section of the site and the intrinsic efficiency for unit incident fluence of radiation;

ii. The important radiosensitive sites in the cell nucleus are the double stranded segments in the nuclear DNA;

iii. The dominant crucial physical parameter of the charged particle radiation is the mean free path between ionization interactions;

iv. Damage is a stochastic process which occurs when the mean spacing between interactions along the charged particle track matches the mean chord distance through a DNA segment (~2nm);

v. Radiation effects depend mainly on the frequency and spatial correlation of interactions, and not on the energy transferred in the interactions;

vi. Damage is predominantly due to intra-track, not inter-track, processes for all radiations except at very large doses. The slope of the probability (P) against the mean free path (λ) for $\lambda > 2$ nm (i.e. the unsaturated region) is near unity (refer to figure 4.1). In other words there is a negligible 'dose rate effect' which is contrary to the current thinking in many proposed models of repair.

4.3.2. Calculation of Absolute Biological Effectiveness (ABE)

The Absolute Biological Effectiveness (ABE) [139], represents the effectiveness of a particular radiation in term of its capability to induce a certain effect in a biological system. In the present work, ABE of a radiation is defined as the mean number of double strand breaks (dsb) produced and remains unrepaired in a particular biological system, per unit incident fluence of primary radiation. The ABE of a radiation can be defined in terms of three biological parameters, namely:

i. the geometrical projected cross-sectional area of the DNA including an 'overlap' factor i.e. $n_o.\sigma_g$;

ii. the cell cycle time; and

iii. a mean recovery time for double strand breaks in the DNA;

and two physical parameters, namely:

i. the charged particle equilibrium fluence; and

ii. the average mean free path for ionization for the energy spectrum of charged particles.

Here, only direct radiation action is assumed to apply. ABE values are calculated according to the following formula:

$$ABE = \sigma_g \Phi_s . \epsilon . n_o \Sigma \frac{1}{t_i} \int_0^{t_i} \exp(-(t_t - t)/t_r)\, dt$$

where

σ_g = projected cross sectional area of the DNA;

Φ_s = secondary charged particle equilibrium fluence per primary interaction per unit volume;

Σ = inverse mean free path for interaction by the incident radiation. (For indirectly ionising radiation gamma and x-rays, $\Sigma = N\sigma_{tr}$ which is the mass energy transfer coefficient);

n_o = mean number of double stranded DNA segments at risk along a random chord through the cell nucleus;

ε = the efficiency with which double strand breaks are induced by the radiation,

i.e. $\varepsilon = [1-\exp(-\lambda_o/\lambda)]$ so that

for $\lambda_o/\lambda \rightarrow 0$; $\varepsilon \rightarrow \lambda_o/\lambda$

and $\lambda_o/\lambda \rightarrow \infty$; $\varepsilon \rightarrow 1$ (saturation):

t_1 = cell cycle time;

t_r = mean repair time for a dsb; and

t_i = duration of irradiation.

For incident fluence of indirectly ionizing radiation, the ABE formula can be rearranged as follows:

$$ABE = (\sigma_g . n_o)\ (\phi_s . \epsilon)\ (N\sigma_{tr})\ \frac{1}{t_i}\int_0^{t_i} \exp\left[-(t_f - t)/t_r\right] dt$$

The net integral fluence (equilibrium electrons) is given by :

$$\Phi_s = \int_0^{\infty} \varphi_s dE = \int_0^{\infty} \varphi\ (E)\ dE$$

The fluence weighted quality of the radiation field (equilibrium electrons) is given by:

$$\Phi_s . \epsilon = \int_0^{\infty} \varphi\ (\lambda)\ \epsilon\ (\lambda)\ d\lambda$$

If ϕ_f is the incident fluence of indirectly ionising radiation, the survival fraction (SF) is given by:

$SF = \exp(-ABE.\phi_f)$

or $\ln(SF) = -ABE.\phi_f$.

If $\phi_f = 1/ABE$, then $SF = 1/e$, which corresponds to the survival fraction equal to 37%. ABE is in units of area and its reciprocal represents the fluence of incidence radiation which will produce 37 % survival fraction.

The fraction of cells, surviving damage because of the direct component of action is given by:

4.3. Revised Dosimetry System

4.3.1. Conceptual and Principles

The foundations of the unified system of dosimetry are as follows [138]:

i. The absolute specification of radiation quality is based on the probability of induction of a specified end-point (e.g. inactivation or mutation) by single charged particle tracks which actually enter the biological target. The relevant charged particles are those in the equilibrium charged particle spectrum generated in the medium by indirectly or directly ionising radiation (see page 142). The probabilities for induction of the specified damage represents the intrinsic efficiencies of action which are absolute measures of the radiation quality. The absolute biological effectiveness (ABE) can be defined in terms of the product of the geometrical cross-section of the site and the intrinsic efficiency for unit incident fluence of radiation;

ii. The important radiosensitive sites in the cell nucleus are the double stranded segments in the nuclear DNA:

iii. The dominant crucial physical parameter of the charged particle radiation is the mean free path between ionization interactions;

iv. Damage is a stochastic process which occurs when the mean spacing between interactions along the charged particle track matches the mean chord distance through a DNA segment (~2nm);

v. Radiation effects depend mainly on the frequency and spatial correlation of interactions, and not on the energy transferred in the interactions;

vi. Damage is predominantly due to intra-track, not inter-track, processes for all radiations except at very large doses. The slope of the probability (P) against the mean free path (λ) for $\lambda > 2$ nm (i.e. the unsaturated region) is near unity (refer to figure 4.1). In other words there is a negligible 'dose rate effect' which is contrary to the current thinking in many proposed models of repair.

4.3.2. Calculation of Absolute Biological Effectiveness (ABE)

The Absolute Biological Effectiveness (ABE) [139], represents the effectiveness of a particular radiation in term of its capability to induce a certain effect in a biological system. In the present work, ABE of a radiation is defined as the mean number of double strand breaks (dsb) produced and remains unrepaired in a particular biological system, per unit incident fluence of primary radiation. The ABE of a radiation can be defined in terms of three biological parameters, namely:

i. the geometrical projected cross-sectional area of the DNA including an 'overlap' factor i.e. $n_o.\sigma_g$;

ii. the cell cycle time; and

iii. a mean recovery time for double strand breaks in the DNA;

and two physical parameters, namely:

i. the charged particle equilibrium fluence; and

ii. the average mean free path for ionization for the energy spectrum of charged particles.

Here, only direct radiation action is assumed to apply. ABE values are calculated according to the following formula:

$$ABE = \sigma_g \Phi_s . \epsilon . n_o \Sigma \frac{1}{t_i} \int_0^{t_i} \exp(-(t_c - t)/t_r)\, dt$$

where

σ_g = projected cross sectional area of the DNA;

Φ_s = secondary charged particle equilibrium fluence per primary interaction per unit volume;

Σ = inverse mean free path for interaction by the incident radiation. (For indirectly ionising radiation gamma and x-rays, $\Sigma = N\sigma_{tr}$ which is the mass energy transfer coefficient);

n_o = mean number of double stranded DNA segments at risk along a random chord through the cell nucleus;

ε = the efficiency with which double strand breaks are induced by the radiation.

i.e. $\varepsilon = [1-\exp(-\lambda_o/\lambda)]$ so that

for $\lambda_o/\lambda \rightarrow 0$; $\varepsilon \rightarrow \lambda_o/\lambda$

and $\lambda_o/\lambda \rightarrow \infty$; $\varepsilon \rightarrow 1$ (saturation);

t_1 = cell cycle time;

t_r = mean repair time for a dsb; and

t_i = duration of irradiation.

For incident fluence of indirectly ionizing radiation, the ABE formula can be rearranged as follows:

$$ABE = (\sigma_g . n_o)\ (\phi_s . \epsilon)\ (N\sigma_{tr})\ \frac{1}{t_i}\int_0^{t_i} \exp\left[-(t_f - t)/t_r\right] dt$$

The net integral fluence (equilibrium electrons) is given by :

$$\Phi_s = \int_0^{\infty} \varphi_s dE = \int_0^{\infty} \varphi\ (E)\ dE$$

The fluence weighted quality of the radiation field (equilibrium electrons) is given by:

$$\Phi_s . \epsilon = \int_0^{\infty} \varphi\ (\lambda)\ \epsilon\ (\lambda)\ d\lambda$$

If ϕ_f is the incident fluence of indirectly ionising radiation, the survival fraction (SF) is given by:

$SF = \exp(-ABE.\phi_f)$

or $\ln(SF) = -ABE.\phi_f$.

If $\phi_f = 1/ABE$, then $SF = 1/e$, which corresponds to the survival fraction equal to 37%. ABE is in units of area and its reciprocal represents the fluence of incidence radiation which will produce 37 % survival fraction.

The fraction of cells, surviving damage because of the direct component of action is given by:

$$\ln (SF) = -\sigma_B \cdot \phi_s \cdot k(t_i)$$

where:

σ_B the biological effect cross-section, represents an absolute quality cross-section (unmodified by repair) of the field radiation that generates an integral fluence of charged particle ϕ_s in an irradiation time t_i;

ϕ_s is the integral fluence of charged particles in an irradiation time t_i; and

$k(t_i)$ is a repair term. It represents the probability that the induced double strand breaks in the cell will be repaired before a stated fixation time t_f.

The biological effect cross-section σ_B is a function of well-defined physical and biological parameters given by;

$$\sigma_B = \sigma_g \cdot n_o \cdot (R/d) \cdot \varepsilon$$

where

σ_g $\approx 4.0 \times 10^{-8}$ cm^2 ; the projected cross-sectional area of intracellular DNA;

n_o is the average number of DNA segments at risk (~15) on penetration of a mean chord traversal of the cell nucleus by a charged particle track;

R/d is the ratio of the mean range R, of the relevant charged particle tracks to the mean chord length d, of the cell nucleus. If R > d, R/d is limited to 1; and

ε is the efficiency with which the charged particle radiation induces double strand breaks.

Inactivation probability (P) is defined as the ratio of the effect cross-section to the geometrical cross-sectional area of the sensitive sites. When P is plotted as a function of the mean free path (λ) for primary ionisation of the relevant charged particle tracks, a unified representation of data can be obtained for all cell types and all heavy particle types (refer to figure 4.1). For indirectly ionising radiation the relevant particles are those in the secondary charged particle equilibrium spectrum. In the ABE calculation, the integral fluence generated by the incident radiation fluence at the point of irradiation of samples e.g. cells, has to be determined.

4.3.2.1. Calculation of ABE for Photons

For photon ABE calculation, it is assumed that the projected geometrical cross-sectional area of the DNA (σ_g) is equal to 4.0×10^{-8} cm^2, and the number of double stranded DNA segments at risk along a random chord through the cell nucleus (n_o)

is equal to 15. Calculation is carried out according to the following formula:

$$ABE=[\sigma_g.(R/d).n_o](\phi_s.\varepsilon)(N.\sigma_{tr})x1.$$

Assume that the repair term is equal to 1 (i.e. only the initial damage is considered) and the other values are obtained from computer calculation (i.e. result from 'pelsld' computer programme). ABE values for various photon energies are calculated by using a computer programme as in appendix one (i.e. photonabef.for) and the values are given in table 4.1 and the graphical illustrations are given in figures 4.2 and 4.4.

4.3.2.2. Calculation of ABE for Neutrons

The effectiveness of neutron irradiation in tissue (i.e. approximated by water) is due to the hydrogen and oxygen recoils induced. The absolute biological effectiveness per unit incident neutron fluence "ABE_{tot}, is the total effectiveness of the recoils, obtained by direct summation and given by the following equation:

$$^nABE_{tot} = {}^nABE_H + {}^nABE_O$$

where

$^nABE_H$ is the total absolute biological effectiveness of the hydrogen recoils; and

$^nABE_O$ is the total absolute biological effectiveness of the oxygen recoils.

i. For Hydrogen Recoils;

$$^nABE_H = [\sigma_g.(R/d).n_o]_H(\phi_s.\varepsilon)_H(N.\sigma_{tr})_H x1$$

where;

σ_g is taken as equal to $\approx 4x10^{-8}$ cm^2;

(R/d) is 1 if R/d>1; and R/d if R/d<1;

n_o for hydrogen recoil is equal to about 15;

ϕ_s is the equilibrium fluence of hydrogen recoils;

ε $\varepsilon=(1-\exp(-\lambda_o/\lambda))$ is calculated by using λ_o=2nm and λ mean free path for primary ionization of H recoil;

$(N.\sigma_{tr})_H$ is for hydrogen recoil which is obtained from the computer calculation. The value has been multiplied by two, in order to take into consideration two hydrogen atoms for each water molecule.

ii. For Oxygen Recoils;

$$^{n}ABE_{O} = [\sigma_{g}.(R/d).n_{o}]_{O}(\phi_{s}.\varepsilon)_{O}(N.\sigma_{tr})_{O}x1$$

where;

σ_g is $4x10^{-8}$ cm^2;

(R/d) is 1 if R/d>1; and R/d if R/d<1;

n_o is equal to about 15;

ϕ_s is the equilibrium fluence of oxygen recoils, generated per unit incident neutron fluence;

ε $\varepsilon=(1-\exp(-\lambda_o/\lambda))$ is calculated by using λ_o=2nm and λ mean free path for primary ionization of oxygen recoils;

$(N.\sigma_{tr})_O$ is the inverse mean free path for oxygen recoils and is obtained from the computer calculation.

For the neutron ABE calculation, a computer programme (i.e. neutronabe.for), as in appendix one is used to calculate ABE values from the outputs of the computer programme (i.e.neutlt.for), which calculates the hydrogen and oxygen recoil equilibrium spectra generated per unit incident neutron fluence and ABE of the recoils. The neutron cross section [140] used is as in appendix one. The ABE values for neutrons with various energies are given in table 4.2 and the graphical illustrations are given in figures 4.3 and 4.4.

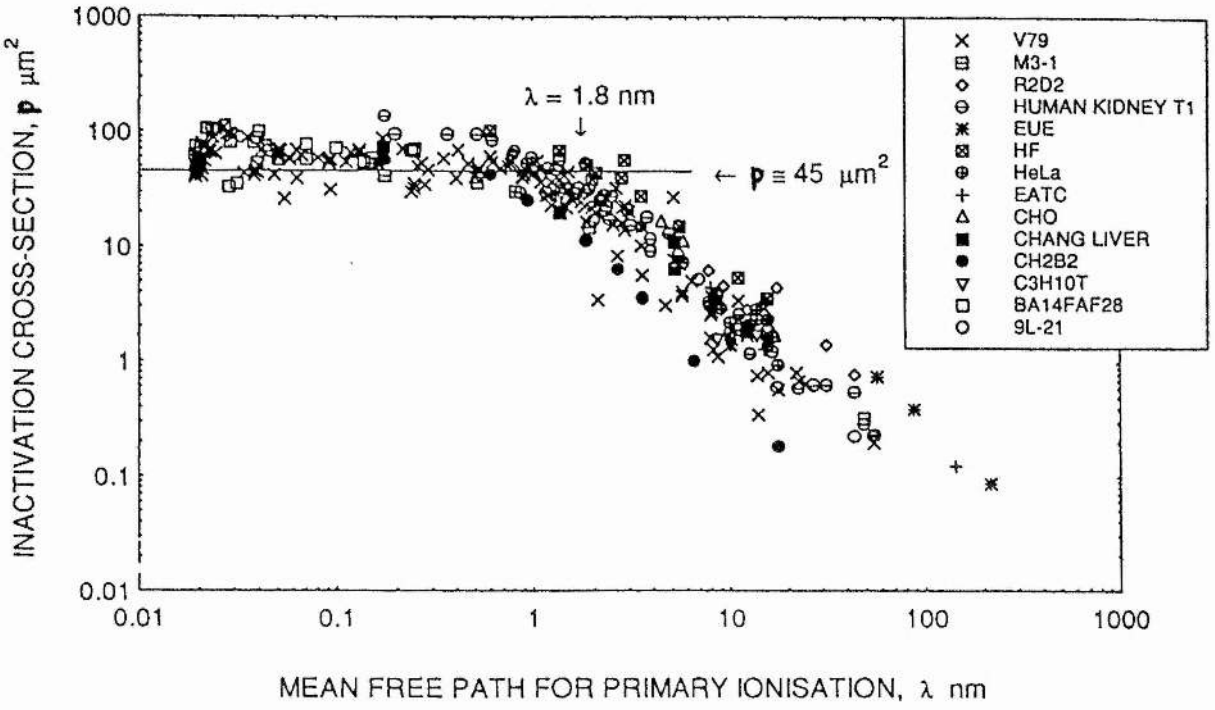


Fig. 4.1: Effect Cross Section (P) against Mean Free Path for Primary Ionisation (λ)

Table 4.1: The Absolute Biological Effectiveness (ABE) of Photons with Various Energies.

Sources	X or Gamma Energy (keV)	ABE for Gamma (cm^2)	Mean Free Path (nm)
C	2.77E-01	1.31E-08	3.35E+00
N	3.92E-01	1.67E-08	3.41E+00
Ne	8.49E-01	3.04E-09	3.38E+00
Al	1.49E+00	2.65E-09	3.97E+00
K	3.31E+00	8.19E-10	5.81E+00
Cr	5.41E+00	3.32E-10	7.89E+00
Mn	5.90E+00	2.78E-10	8.00E+00
Fe	6.40E+00	2.37E-10	8.81E+00
Co	6.92E+00	2.03E-10	9.26E+00
Cu	8.04E+00	1.49E-10	1.01E+01
Zn	8.63E+00	1.28E-10	1.05E+01
Ge	9.88E+00	9.57E-11	1.11E+01
As	1.05E+01	8.33E-11	1.14E+01
Se	1.12E+01	7.23E-11	1.17E+01
Br	1.19E+01	6.35E-11	1.19E+01
Sr	1.41E+01	4.21E-11	1.18E+01
Zr	1.58E+01	3.21E-11	1.16E+01
Mo	1.74E+01	2.44E-11	1.09E+01
Ag	2.21E+01	1.20E-11	9.09E+00
Cd	2.31E+01	1.05E-11	8.70E+00
Te	2.74E+01	5.88E-12	7.61E+00
Ba	3.21E+01	3.39E-12	6.94E+00
Sm	3.99E+01	1.62E-12	6.62E+00
Tm	5.04E+01	8.68E-13	6.94E+00
W	5.88E+01	6.72E-13	7.41E+00
Am	5.96E+01	6.63E-13	7.51E+00
Au	6.81E+01	6.07E-13	8.12E+00

Sources	X or Gamma Energy (keV)	ABE for Gamma (cm^2)	Mean Free Path (nm)
Bi	7.62E+01	6.09E-13	8.77E+00
U	9.70E+01	7.57E-13	1.06E+01
Cs	6.61E+02	1.74E-11	6.31E+01
Co	1.25E+03	5.68E-11	1.04E+02

Table 4.2: The Absolute Biological Effectiveness (ABE)[9] of Neutron with Various Energies.

Neutron Energy (keV)	ABE for Neutrons (cm^2)	Mean free path for Hydrogen recoil(nm)	Mean free path for Oxygen recoil (nm)
1.00E-01	6.43E-13	3.11E+01	9.83E-08
1.50E-01	9.44E-13	2.39E+01	1.26E-07
2.00E-01	1.23E-12	1.96E+01	1.40E-07
3.00E-01	1.77E-12	1.49E+01	1.54E-07
4.00E-01	2.28E-12	1.22E+01	1.60E-07
5.00E-01	2.77E-12	1.05E+01	1.64E-07
6.00E-01	3.23E-12	9.29E+00	1.67E-07
7.00E-01	3.69E-12	8.38E+00	1.69E-07
8.00E-01	4.11E-12	7.69E+00	1.70E-07
9.00E-01	4.53E-12	7.11E+00	1.72E-07
1.00E+00	4.93E-12	6.65E+00	1.73E-07
1.50E+00	6.77E-12	5.17E+00	1.79E-07
2.00E+00	8.37E-12	4.36E+00	1.84E-07
3.00E+00	1.12E-11	3.47E+00	1.92E-07
4.00E+00	1.36E-11	2.97E+00	2.01E-07
5.00E+00	1.57E-11	2.66E+00	2.10E-07
6.00E+00	1.75E-11	2.43E+00	2.18E-07
7.00E+00	1.92E-11	2.27E+00	2.26E-07
8.00E+00	2.06E-11	2.13E+00	2.34E-07
9.00E+00	2.19E-11	2.03E+00	2.43E-07
1.00E+01	2.33E-11	1.94E+00	2.51E-07
1.50E+01	2.81E-11	1.67E+00	2.89E-07
2.00E+01	3.11E-11	1.52E+00	3.27E-07
3.00E+01	3.59E-11	1.37E+00	4.04E-07

[9] Note for γ-rays n~15 also, but λ is much larger than for neutron induced recoils and R/d plays a role.

Neutron Energy (keV)	ABE for Neutrons (cm^2)	Mean free path for Hydrogen recoil(nm)	Mean free path for Oxygen recoil (nm)
4.00E+01	3.84E-11	1.30E+00	4.81E-07
5.00E+01	4.06E-11	1.26E+00	5.59E-07
6.00E+01	4.17E-11	1.24E+00	6.39E-07
7.00E+01	4.23E-11	1.23E+00	7.18E-07
8.00E+01	4.22E-11	1.22E+00	7.97E-07
9.00E+01	4.23E-11	1.21E+00	8.72E-07
1.00E+02	4.21E-11	1.21E+00	9.54E-07
1.50E+02	4.04E-11	1.22E+00	1.35E-06
2.00E+02	4.00E-11	1.26E+00	1.78E-06
3.00E+02	4.07E-11	1.37E+00	2.93E-06
4.00E+02	4.10E-11	1.51E+00	1.43E-05
4.40E+02	4.09E-11	1.57E+00	1.04E-05
5.00E+02	4.11E-11	1.67E+00	5.79E-06
6.00E+02	4.25E-11	1.83E+00	5.80E-06
7.00E+02	4.42E-11	2.00E+00	6.97E-06
8.00E+02	4.55E-11	2.17E+00	8.77E-06
9.00E+02	4.81E-11	2.34E+00	1.87E-05
1.00E+03	5.01E-11	2.52E+00	2.20E-05
1.50E+03	5.83E-11	3.40E+00	1.58E-05
2.00E+03	6.61E-11	4.32E+00	1.74E-05
3.00E+03	8.17E-11	6.14E+00	5.16E-05
3.75E+03	8.58E-11	7.54E+00	7.97E-05
4.00E+03	8.77E-11	8.01E+00	6.77E-05
5.00E+03	9.30E-11	9.85E+00	6.89E-05
6.00E+03	9.68E-11	1.17E+01	6.97E-05
7.00E+03	1.00E-10	1.36E+01	7.69E-05
8.00E+03	1.01E-10	1.55E+01	7.42E-05
9.00E+03	1.02E-10	1.74E+01	9.68E-05

Neutron Energy (keV)	ABE for Neutrons (cm^2)	Mean free path for Hydrogen recoil(nm)	Mean free path for Oxygen recoil (nm)
1.00E+04	1.13E-10	1.93E+01	1.61E-04
1.50E+04	1.09E-10	2.88E+01	4.32E-04
2.00E+04	1.03E-10	3.84E+01	8.36E-04
3.00E+04	8.74E-11	5.80E+01	1.50E-03
4.00E+04	7.91E-11	7.75E+01	2.14E-03
5.00E+04	7.00E-11	9.59E+01	2.69E-03
6.00E+04	6.11E-11	1.14E+02	3.17E-03
7.00E+04	5.56E-11	1.31E+02	3.67E-03
8.00E+04	6.65E-11	1.49E+02	4.17E-03
9.00E+04	7.77E-11	1.66E+02	4.64E-03
1.00E+05	8.87E-11	1.84E+02	5.17E-03

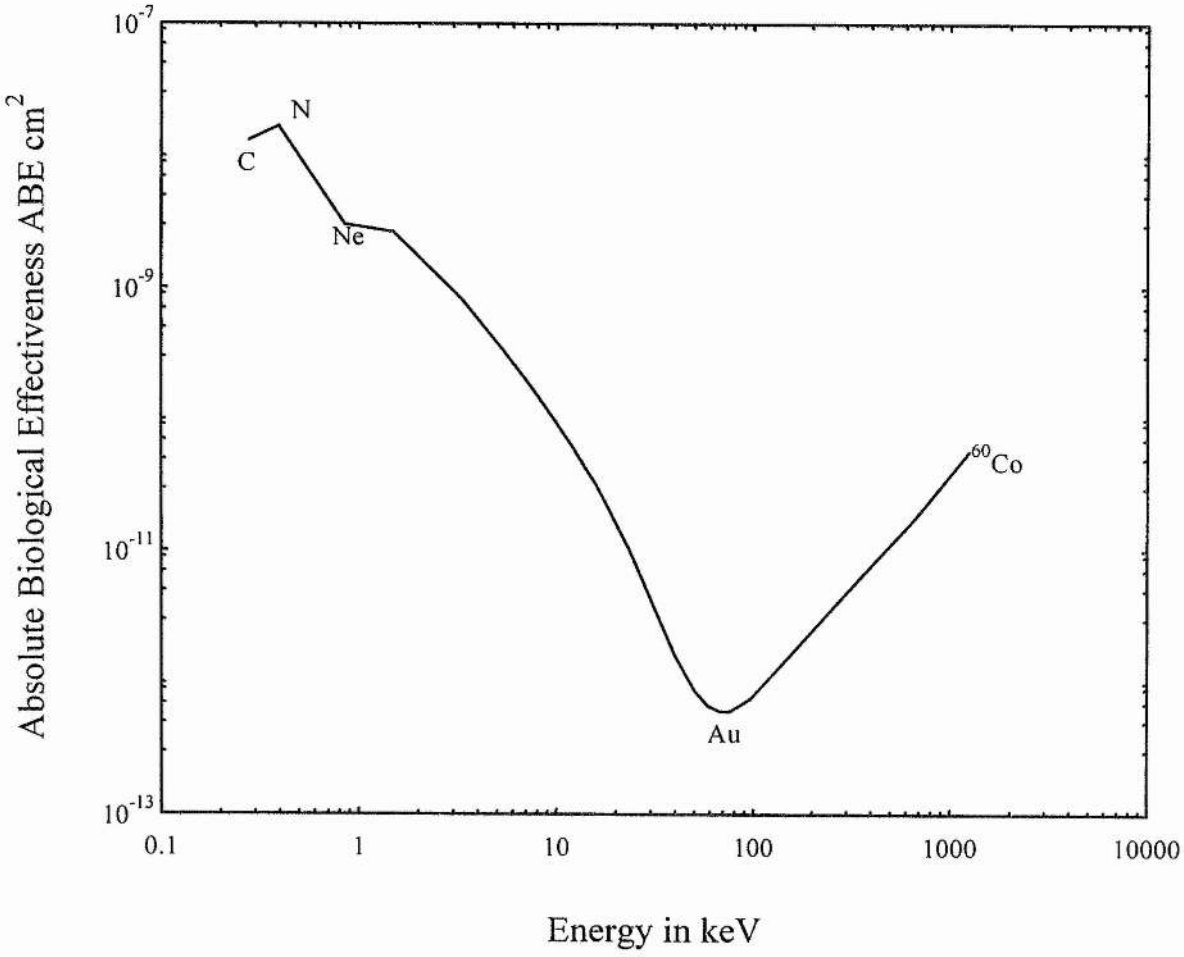


Fig. 4.2: ABE for Photon (cm^2) for various Energies in keV

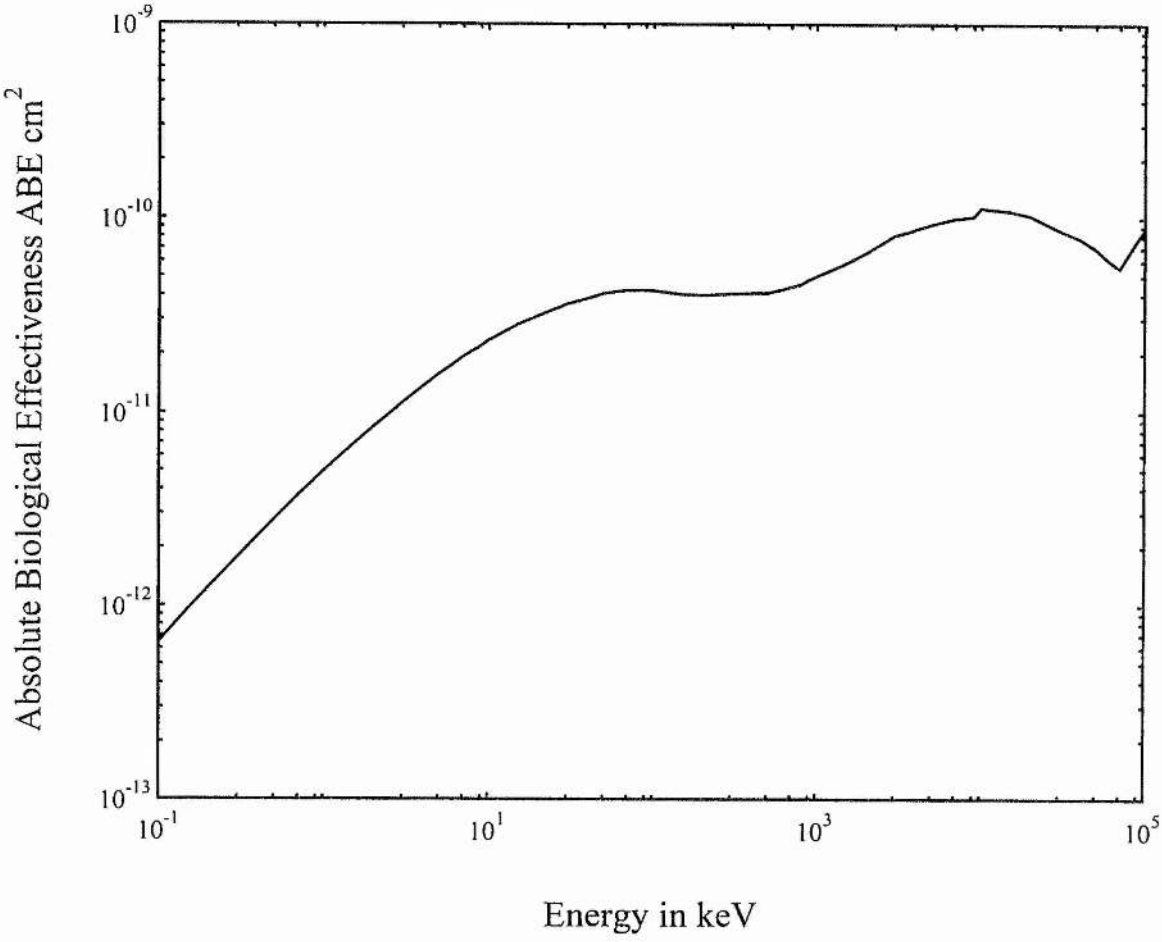


Fig. 4.3: ABE for Neutron (cm^2) for various Neutron Energies in keV

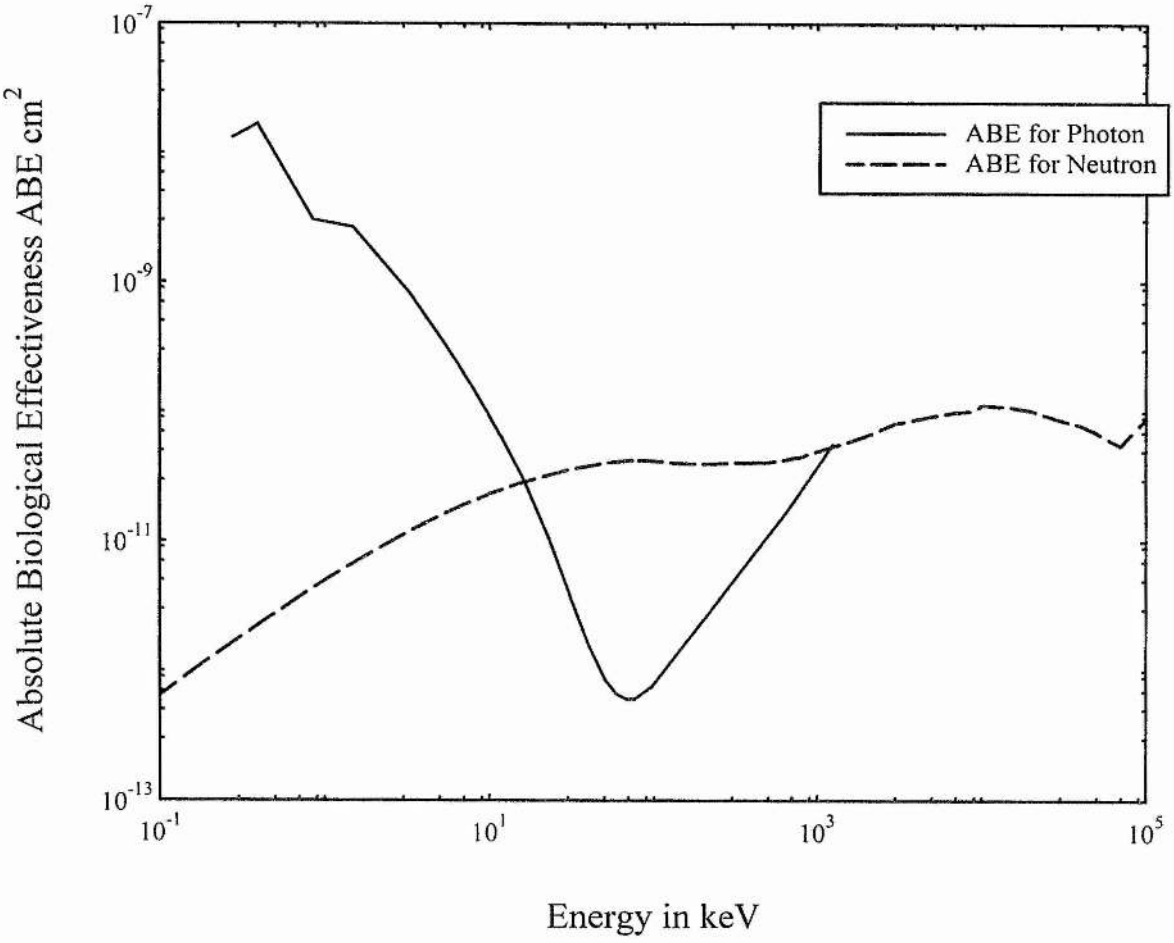


Fig. 4.4: ABE for Photon and Neutron (cm^2) Against Energies in keV

Table 4.3: Irradiation Cases

Cases	Mono-energetic or spectrum	Charged Particle Equilibrium (CPE) or Track Segment Experiment	Remarks
External Photons ϕ_i is the incident Fluence	Mono-energetic	Charged Particle Equilibrium The integral fluence ϕ_s is equal to $\phi_v.\mu.\phi_i$ where ϕ_v is the equilibrium fluence of charged particles generated per interaction per unit volume; μ is the interaction coefficient for the indirectly ionising radiation in the medium; and ϕ_i is the incident fluence	i.The DNA double strand in the DNA segment is assumed to be the sensitive site. ii. Spacing between the primary ionisations along the charged particle track in the medium or sample is shown to represent the quality of the radiation track. i and ii must match for the maximum effect i.e the effect probability corresponds to $(1-\exp(\lambda_0/\lambda))$
	Complex incident photon spectrum (which includes x-rays, γ-spectrum from radionuclides) can be written as $\Sigma_{hv=min}^{max}(\phi_{hv,i})$.	Charged Particle Equilibrium The integral fluence is the numerical integration of the spectrum; $\Sigma_{j=hv} f\ \phi_{sec,j}\mu_j\ \phi_{i,j}$	
External neutrons ϕ_i;the incident Fluence	Mono-energetic	Charged Particle Equilibrium The integral fluence is equal to $\phi_v.(N_H\sigma_{nH})\phi_i$ where ϕ_v is the equilibrium fluence of charged particles generated per interaction per unit volume; $(N_H\sigma_{nH})$ is the interaction coefficient for the neutrons in the medium; and ϕ_i is the incident fluence	

Cases	Mono-energetic or spectrum	Charged Particle Equilibrium (CPE) or Track Segment Experiment	Remarks
	Spectrum	Charged Particle Equilibrium The integral fluence is the numerical integration of the spectrum: $\Sigma_{i,j}[f\phi_{sec,j}(N_H\sigma_{nH})_j \phi_{i,j}]$ where f is the fraction of the jth component.	
External Heavy Ions (HZE)	Mono-energetic	Track segment experiment (instantaneous values)	
Internal Radionuclides α, β, and γ emitters	Sufficiently homogeneously distributed (except special cases electron capture and auger electron) in the medium or samples	$\phi_s = \phi_v.C$ $\phi_v = R_p.F_s$. where: ϕv is the equilibrium fluence of charged particles generated per unit source strength. C is the concentration of source activity in the sample. R_p is the range of the frequency weighted average energy of primary charged particles representing the decay spectrum emitted by the source activity of concentration C. F_s is the build up ratio of secondary to primary charged particle fluence. F_s takes care of the contribution from secondary, tertiary etc.	

4.4. Interpretation and Discussion

4.4.1. The expression of Risk in term of ABE

Risk is expressed per unit Sievert (Sv), namely $4x10^{-2}$ Sv^{-1} for persons occupationally exposed which corresponds to a dose limit of 20 mSv per year and $5x10^{-2}$ Sv^{-1} for members of the general population which corresponds to a dose limit of 1 mSv per year (see page 137). The Equivalent Dose H, in Sievert is the sum of absorbed dose D, multiplied by the radiation weighting factor w_R, according to the following formula:

$$H= D_{\gamma}.(w_R)_{\gamma} + D_n.(w_R)_n$$

(i.e. replacing the previous formula for the dose equivalent H, $H=D_{\gamma}Q_{\gamma} + D_n.Q_n$ where $Q_{\gamma}=1$ and $Q_n=10$ are the quality factors for gamma-rays and neutrons respectively). For γ rays $w_R=1$ irrespective of its energy and for neutrons, w_R varies. It is equal to 5, 10, 20, 10 and 5 for neutron energies less than 10, 10-100, 100-2000, 2000-20000, and greater than 20000 keV respectively (see table 1.6). For neutron energies of 0.3 (for Hiroshima) and 1.6 MeV (for Nagasaki), w_R is equal to 20. The average gamma-ray energy for Hiroshima and Nagasaki is assumed to be equal to 1.0 MeV.

In order to express risk in terms of ABE (i.e.the unified system of dosimetry) the following information is required:

i. the ratio between component doses (i.e. γ and neutron) to the total doses; and

ii. the energy of the radiation from which ABE and LET can be deduced.

The Sievert can be resolved into its components such as gamma dose and neutron dose. The total effectiveness (BE_{total}) of a radiation field (γ and neutron) is given by:

$$BE_{total} = \phi_n.ABE_n + \phi_{\gamma}.ABE_{\gamma}$$

where;

ϕ_n is the neutron fluence;

ABE_n is the absolute biological effectiveness per unit incident neutron fluence;

ϕ_{γ} is the gamma fluence; and

ABE_{γ} is the absolute biological effectiveness per unit incident gamma fluence.

From the epidemiological study of Japanese survivors, the ratios between gamma dose (f_{γ}) and neutron dose (f_n) against total dose received by the survivors, vary

depending on many factors such as shielding, slant distance from explosion point, transmission factor etc. It is reasonable to assume that f_γ varies subject to the general characteristics of the radiation fields in Hiroshima and Nagasaki (refer to figure 4.5). In the following exercise, for simplification it is assumed that the total dose (i.e. gamma and neutron dose) is equal to 1 Sv. Also for simplification, only three values of f_γ are considered, namely 1.0, 0.90 and 0.75. The fluence ϕ can be deduced from the expression $D=\phi.L$, by using L values from the reference data [141][142][143].

4.4.1.1. In Hiroshima

i. f_γ=1.0; D= 1.0 Sv; E_γ=1000 keV and E_n=300 keV.

H_γ=1.0 Sv and H_n =(1-1) = 0.0 Sv. By using w_R equal to 1 and 20 for gamma and neutron respectively, D_γ=1.0 Sv and D_n=0.00 Sv. For the present purpose, 1 Sv must be expressed in terms of BE. To do this, the energy and the flux must be known. For the gamma dose $D_\gamma = \phi_\gamma.L$, from the table L= 0.378 keVμm^{-1}. For neutron $D_n = \phi_n.L$, since D_n=0.00 so ϕ_n=0.00 .

By using formula $BE_{total}=\phi_\gamma.ABE_\gamma + \phi_n.ABE_n$;

$\phi_\gamma.ABE_\gamma$ =(1.0/L) x ABE_γ(energy 1.0 MeV)

= (1.0/0.378) x 3.75xE-11=9.92E-11

$\phi_n.ABE_n$ =(0.0/L) x ABE_n(energy 0.3 MeV)= 0.00

BE_{total} =9.92E-11.

i. For radiation workers (i.e. dose limit of 20 mSv per year, which corresponds to the risk factor of $4x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $4x10^{-2}$ / 9.92E-11

= 4.03E+08 $(BE)^{-1}$

ii. For a member of the general public (i.e. dose limit 1 mSv per year, which corresponds to the risk factor of $5x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $5x10^{-2}$ / 9.92E-11

= 5.04E+08 $(BE)^{-1}$.

The risk factor is equal to 4.03E+08 $(BE)^{-1}$ and 5.04E+08 $(BE)^{-1}$ for a radiation worker and a member of the general public respectively.

ii. f_γ=0.9; D= 1.0 Sv; E_γ=1000 keV and E_n=300 keV

H_γ=0.9 Sv and H_n =(1-0.9) = 0.1 Sv. By using w_R equal to 1 and 20 for gamma and neutron respectively, D_γ=0.9 Sv and D_n=0.1/20=0.005 Sv. For the present purpose, 1 Sv must be expressed in terms of BE. To do this, the energy and the flux must be known. For gamma dose $D_\gamma = \phi_\gamma.L$, from the table L= 0.378 keVμm^{-1}. For neutron $D_n = \phi_n.L$, from the table for E_n=300 keV, L=66.34 keVμm^{-1}.

By using formula $BE_{total}=\phi_\gamma.ABE_\gamma + \phi_n.ABE_n$;

$\phi_\gamma.ABE_\gamma$ =(0.9/0.378)x3.75E-11 = 8.93E-11.

$\phi_n.ABE_n$ =(0.005/66.34)x 3.95E-11= 2.98E-15.

BE_{total} = 8.93E-11 + 2.98E-15 = 8.93E-11.

i. For radiation workers (i.e. dose limit of 20 mSv per year, which corresponds to the risk factor of 4x10^{-2}) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = 4x10^{-2} / 8.93E-11.

= 4.48E+08 (BE)$^{-1}$

ii. For a member of the general public (i.e. dose limit 1 mSv per year, which corresponds to the risk factor of 5x10^{-2}) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = 5x10^{-2} / 8.93E-11.

= 5.60E+08 (BE)$^{-1}$.

The risk factor is equal to 4.48E+08 (BE)$^{-1}$ and 5.60E+08 (BE)$^{-1}$ for a radiation worker and a member of the general public respectively.

iii. f_γ=0.75; D= 1 Sv; E_γ=1000 keV and E_n=300 keV.

H_γ=0.75 Sv and H_n =(1-0.75) = 0.25 Sv. By using w_R equal to 1 and 20 for gamma and neutron respectively, D_γ=0.75 Sv and D_n=0.25/20=0.0125 Sv. For the present purpose, 1 Sv must be expressed in terms of BE. To do this, the energy and the flux must be known. For gamma $D_\gamma = \phi_\gamma.L$, from the table L= 0.378 keVμm^{-1}. For neutron $D_n = \phi_n.L$, from the table L= 66.34 keVμm^{-1}.

By using $BE_{total}=\phi_\gamma.ABE_\gamma + \phi_n.ABE_n$

$\phi_\gamma.ABE_\gamma$ =(0.75/0.378)x3.75E-11=7.44E-11.

$\phi_n.ABE_n$ =(0.0125/66.34)x3.95E-11=7.44E-15.

BE_{total} = 7.44E-11.

i. For radiation workers (i.e. dose limit of 20 mSv per year, which corresponds to the risk factor of $4x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $4x10^{-2}$ / 7.44E-11 =5.38E+08.

= 5.38E+08 $(BE)^{-1}$

ii. For a member of the general public (i.e. dose limit 1 mSv per year, which corresponds to the risk factor of $5x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $5x10^{-2}$ / 7.44E-11 =6.72E+08.

The risk factor is equal to 5.38E+08 $(BE)^{-1}$ and 6.72E+08 $(BE)^{-1}$ for a radiation worker and a member of the general public respectively.

4.4.1.2. In Nagasaki

By carrying out the same calculation, using data listed in table 4.4, for neutron energy equal to 1.6 MeV, the results are as shown in table 4.6. The parameters used in the calculations to express risk in the unified system of dosimetry are listed in table 4.4.

The calculations are summarised as follows:

i. f_γ=1.0; D= 1.0 Sv; E_γ=1000 keV and E_n=1600 keV.

By using formula $BE_{total}=\phi_\gamma.ABE_\gamma+\phi_n.ABE_n$;

$\phi_\gamma.ABE_\gamma$ =(1.0/L) x ABE_γ(energy 1.0 MeV)

= (1.0/0.378) x 3.75xE-11=9.92E-11

$\phi_n.ABE_n$ =(0.0/L) x ABE_n(energy 0.3 MeV)= 0.00

BE_{total} =9.92E-11.

i. For radiation workers (i.e. dose limit of 20 mSv per year, which corresponds to the risk factor of $4x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $4x10^{-2}$ / 9.92E-11

= 4.03E+08 $(BE)^{-1}$

ii. For a member of the general public (i.e. dose limit 1 mSv per year, which corresponds to the risk factor of $5x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $5x10^{-2}$ / 9.92E-11

= 5.04E+08 $(BE)^{-1}$.

The risk factor is equal to 4.03E+08 $(BE)^{-1}$ and 5.04E+08 $(BE)^{-1}$ for a radiation worker and a member of the general public respectively.

ii. f_γ=0.9; D= 1.0 Sv; E_γ=1000 keV and E_n=1600 keV

By using formula $BE_{total}=\phi_\gamma.ABE_\gamma + \phi_n.ABE_n$;

$\phi_\gamma.ABE_\gamma$ =(0.9/0.378)x3.75E-11 = 8.93E-11.

$\phi_n.ABE_n$ =(0.005/40.47)x 6.06E-11= 7.49E-15.

BE_{total} = 8.93E-11 + 7.49E-15 = 8.93E-11.

i. For radiation workers (i.e. dose limit of 20 mSv per year, which corresponds to the risk factor of $4x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $4x10^{-2}$ / 8.93E-11.

= 4.48E+08 $(BE)^{-1}$

ii. For a member of the general public (i.e. dose limit 1 mSv per year, which corresponds to the risk factor of $5x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $5x10^{-2}$ / 8.93E-11.

= 5.60E+08 $(BE)^{-1}$.

The risk factor is equal to 4.48E+08 $(BE)^{-1}$ and 5.60E+08 $(BE)^{-1}$ for a radiation worker and a member of the general public respectively.

iii. f_γ=0.75; D= 1 Sv; E_γ=1000 keV and E_n=1600 keV.

By using $BE_{total}=\phi_\gamma.ABE_\gamma + \phi_n.ABE_n$

$\phi_\gamma.ABE_\gamma$ =(0.75/0.378)x3.75E-11=7.44E-11.

$\phi_n.ABE_n$ =(0.0125/40.47)x6.06E-11=1.87E-15.

BE_{total} = 7.44E-11.

i. For radiation workers (i.e. dose limit of 20 mSv per year, which corresponds to the risk factor of $4x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $4x10^{-2}$ / 7.44E-11 =5.38E+08.

= 5.38E+08 $(BE)^{-1}$

ii. For a member of the general public (i.e. dose limit 1 mSv per year, which corresponds to the risk factor of $5x10^{-2}$) the risk factor in terms of ABE is equal to R_{ABE}:

R_{ABE} = $5x10^{-2}$ / 7.44E-11 =6.72E+08.

The risk factor is equal to 5.38E+08 $(BE)^{-1}$ and 6.72E+08 $(BE)^{-1}$ for a radiation worker and a member of the general public respectively.

Information on the atomic bombs dropped at Hiroshima and Nagasaki [144] is listed in table 4.5.

Table 4.4: The parameters used to express risk in the unified system of dosimetry

Type	Energy (keV)	ABE (cm^2)	LET ($keV\mu m^{-1}$)		Fluence (cm^{-2})	
			$L_{T,H}$, hydrogen recoil	$L_{T,O}$ oxygen recoil	Hydrogen recoil	Oxygen recoil
Recoils of neutron	300		64.11	200.50	1.287×10^{-4}	2.135×10^{-6}
	1600		38.42	260.22	4.75×10^{-4}	4.44×10^{-6}
Neutrons[10]	300	3.95E-11	66.34			
	1600	6.06E-11	40.47			
Gamma[11]	1000	3.75E-11	0.378			

[10] The mean neutron energies in Hiroshima and Nagasaki are assumed equal to 300 keV and 1600 keV respectively.

[11] The mean gamma energies in both Hiroshima and Nagasaki are assumed equal to 1000 keV.

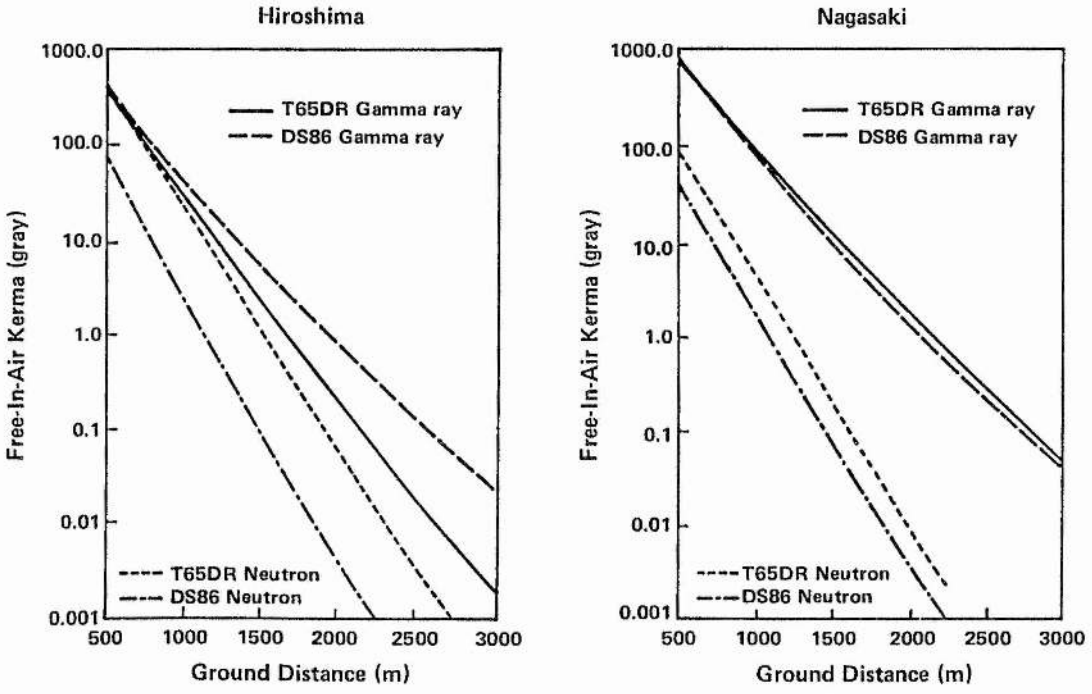


Fig. 4.5: Comparison of values for the radiation fields in the open at Hiroshima and Nagasaki

Table 4.5: The Atomic Bombs dropped in Hiroshima and Nagasaki

Information	Hiroshima	Nagasaki
Date of bombing	6 th. August 1945	9 th. August 1945
Estimated yield	15 ± 3 ktons	22 ± 2 ktons
Average Neutrons energy	0.3 MeV	1.6 MeV
Extrapolated G_o at burst point (m^2rad) Neutron Gamma	 8.7×10^{10} 3.45×10^{10}	 1.30×10^{10} 2.75×10^{10}
H height of burst (m)	570	500
Relaxation length (m) Neutron Gamma	 198 250	 198 350
Type	Uranium (^{235}U) bomb: a gun assembly weapon	Plutonium (^{239}Pu) bomb: an implosive type weapon
General notes: i. In Hiroshima an explosive propellant is used to shoot one piece Uranium against another piece to create a critical mass; and ii. In Nagasaki chemical explosive was used to compressed a subcritical mass to become a critical mass.		

Table 4.6: The Risk Factors expressed in terms of the unified system of dosimetry (i.e. ABE)

Data	Fraction of Gamma Dose	Fraction of Neutron Dose	Risk Factors $(BE)^{-1}$	
			A radiation worker	A member of the public
Hiroshima data	1.00	0.00	4.03E+08	5.04E+08
	0.90	0.10	4.48E+08	5.60E+08
	0.75	0.25	5.38E+08	6.72E+08
Nagasaki data	1.00	0.00	4.03E+08	5.04E+08
	0.90	0.10	4.48E+08	5.60E+08
	0.75	0.25	5.38E+08	6.72E+08
Average for both cities	1.00		4.03E+08	5.04E+08
	0.9		4.48E+08	5.60E+08
	0.75		5.38E+08	6.72E+08

4.4.1.3. Dose Estimation for Japanese Survivors

Dose received by each Japanese survivor was first estimated by using Tentative 1965 Dosimetry System (T65D) and then was estimated by using Dosimetry system 1986 (DS86). Two important parameters for dosimetry of individual survivor are distance and shielding.

In Tentative Dosimetry (T65D) System, gamma and neutron doses received by the survivors are calculated according to the following formula:

$$D(R) = \frac{G_o \exp(-\frac{R}{L})}{R^2}$$

where

D(R) is free in air (FIA) dose in rad;

R is slant distance i.e. between air zero to location at time of explosion;

L is relaxation length in meters (m);

G_o is the intensity in rad.m^2;

$R=(H^2 + d^2)^{1/2}$;

H is the distance between air zero to ground zero: and

d is the distance between ground zero to location at time of explosion.

In T65D the survivor's shielding at the time of bombing (ATB) was taken into account by the use of transmission factor (TF) (i.e. the ratio between the radiation dose inside and outside of the house).

$k_{total}=k(n) + k(\gamma)$

$k(n)=TF(n)k_o(n)$

$k(\gamma)=TF(\gamma)k_o(\gamma)$

where $k_o(n)$ and $k_o(\gamma)$ are radiation doses in the open (outside the house) for neutron and gamma respectively. TF was determined by the nine parameter method, the globe method and ad-hoc assignment method. T65D tissue-kerma estimates for the survivors, served only as an approximation to the maximum absorbed dose at the surface (or skin) of the body.

In 1970 Absorbed Dose Factor (ADF) (i.e. the ratio between absorbed dose in a specific organ and tissue kerma in air) was calculated. The absorbed dose D of an

organ of interest:

$D_{total} = D(n) + d(\gamma)$

$D(n) = ADF(n)\ k(n)$

$D(\gamma) = ADF(\gamma).k(\gamma) + ADF(\gamma\leftarrow)k(n)$

where

ADF(n)k(n) provides the high LET absorbed dose for neutron;

ADF(γ).k(γ) provides the low LET absorbed dose for external γ ray;

ADF(γ←)k(n) provides the low LET absorbed dose from γray produced by neutron interactions within the body (called autogammas)

For leukaemia the organ of interest is active bone mirror. Other cancers, the organ of interest are the female breast, thyroid, lung etc.

The latest dose estimate received for each survivor in Hiroshima and Nagasaki epidemiological studies is carried out by using dosimetry system 1986 (DS86) [145]. The DS86 methods for dose estimation to individual survivors, are embodied in the modular code system as follows:

i. a data base for the radiation fields in the open, which specify the differential energy and angular fluence of neutrons and gamma rays at four different heights above the ground and at 25 m intervals from 100 to 2500 m ground range in both cities;

ii. a data base from home shielding which describes how the differential neutrons and gamma ray fluences are modified at over 50 sites inside, outside and either partially or totally shielded by a Japanese house; and

iii. a data base for organ dosimetry which describes how the differential neutrons and gamma fluences are further modified at 15 organ sites within the body as functions of a survivor's orientation and posture.

DS86 doesn't employ transmission factors (TF) or absorbed dose factor (ADF). For survivors with shielding histories, organ dose and tissue kerma in air were computed directly for cases such as:

i. the survivor was exposed inside a Japanese home and nine parameter data were available;

ii. the survivor was exposed outside but shielded by a japanese house and globe data were available;

iii. the survivor was outside-unshielded and flash burns were reported on exposed portions of the skin (e.g. the face, neck and arm)

4.4.2. Discussion

ABE is energy dependent. From figure 4.2 the ABE values for photons vary from $2x10^{-7}$ cm^2 to $6x10^{-13}$ cm^2 in the energy range from 0.1 keV to 10^5 keV. It has a minimum value about $6x10^{-13}$ cm^2 at an energy of about 70 keV. From figure 4.3 the ABE values for neutrons vary from $2x10^{-10}$ cm^2 to $6x10^{-13}$ cm^2 for neutrons in the energy range from 0.1 to 10^5 keV. If measurement were carried out by using the proposed unified dosemeter, the measurement would be given in BE units which would be directly relatable to the probability of inducing cancer in the person's life. Further study is required to validate this conclusion.

The numerical values for risk per year expressed in both systems, depend on the components of the radiation received. The conversion of risk per year expressed in the conventional dosimetry system into the unified dosimetry system is given in the following example:

> A radiation worker has received the dose limit of 20 mSv per year so the associated risk per year is equal to $20x10^{-3}x4x10^{-2} = 8x10^{-4}$. The cancer risk coefficient is equal to $4x10^{-2}$ Sv^{-1}. In the unified system, the 20 mSv has to be expressed in BE which depends on its fluence components (i.e. fraction of gamma and neutron doses) and, say it is equal to x_1 BE. Then, the risk per year in the unified system is equal to x_1 multiplied by the appropriate risk factor R_{ABE}.

In the LSS study each individual dose is calculated according to the DS86 (Dosimetry System 1986). The individual dose can be expressed in term of BE by carrying out the same procedure as in section 4.4.1. For the whole LSS study cohorts, reassessment of cancer risk in term of the new dosimetry system can be carried out and the result would be given in risk factor per BE. In the examples given to express risk factor in terms of BE, the results in both cities Hiroshima and Nagasaki are the same because the contribution of neutron components are insignificant.

CHAPTER FIVE
CONCLUSION, DISCUSSION AND RECOMMENDATIONS FOR FUTURE WORK

5.1. Conclusions and Discussions

In Radiological Protection near environmental level, the effect of radiation on individual cells can be considered as due to a single track without any saturation effect or inter-track action. Direct data on human beings exposed to low level radiation cannot be obtained mainly due to statistical limitation and the uncertainty is very significant. Radiation risk of significant important in this level is attributable to cancer and genetic effects. Data are obtained mainly from epidemiology studies, ankylosing spondylitis patients, occupational and accidental exposures and animal studies. The most important data is from epidemiological study of Japanese survivors of atomic bombs dropped in Hiroshima and Nagasaki.

This thesis basically presents three main themes namely:

i. Biophysical models of radiation action;

ii. Cancer risk coefficients; and

iii. A proposed new system of dosimetry in terms of ABE.

Five main biophysical models of radiation action have been evaluated and appraised as in chapter two. Cancer risk coefficients, basically from the ICRP assessment, have been presented in chapter three and the proposed new system of dosimetry is explained in chapter four.

5.1.1. Biophysical Modelling

The success in biophysical modelling of radiation damage is believed to rely on the reliability of the physical description of the radiation field and the biological description of the system. As explained in chapter two Harder uses $L_{100,D}$ as a quality parameter and Curtis uses local dose to induce lesions which are able to interact pairwise in the contact regions. Katz uses z^2/β^2 which is interpreted to be the yield of δ-rays per unit track length. Watt interprets z^2/β^2 as the yield of primary ionisations along the track concluding that the δ-ray effects are negligible for fast heavy ions. Bond and Varma use a microdosimetry concept (i.e. hit sizes) to

determine the fraction of cells which responds quantally. Each model has been tested against experimental data and to some extent has achieved its respective goal.

Biophysical modelling carried out in this university (i.e. the TC model) has distinct advantages which include:

i. λ which is used as the quality parameter, has a clear physical interpretation namely the mean free path of the primary ionizations along the particle track;

ii. Fluence of the relevant charged particles (see table 4.3) which is found to be a better field quantity than dose. The effect on cells is determined by the actual number of charged particles traversing the cells multiplied by their probability (cross-section) to induce the effect; and

iii. ABE is used to incorporate the necessary relevant concepts important in modelling, such as;

   a. DNA double strands;

   b. Number of segments at risk along the charged particle track;

   c. Range i.e. R/d factor which indicate the physical capability of any charged particle to penetrate a cell nucleus;

   d. The equilibrium charged particle fluence which is the fundamental cause of the effects;

   e. The concept of cross section which is used to indicate the probability that a charged particle will induce a certain effect; and

   f. The efficiency ε, which indicates the efficiency of the spatially correlated events with the structure of the DNA double strands, to induce DNA dsb.

These factors are deduced directly from the biological observations rather than by mechanistic modelling. The TC model has been applied for many cases such as irradiation by x-ray, γ-ray, heavy ions and electrons. Jin et-al [146] take care of Auger electron cascades as well as photo-electric and Compton electrons in the fluence generated and apply the TC model to yeast cells. Sykes et-al [147] provides interpretation on the reverse dose-rate effects, by using the TC model. In the future the new data obtained by using the latest technique and procedures may be applied in the TC model. An image cytometry device [148] has been

reported to be able to determine with 98% accuracy by automated scanning procedures for cell survival measurements at low doses. The premature chromosome condensation technique (refer to page 32), provides the initial number of DNA dsb in an irradiated system. However it is more meaningful if the data used in modelling are standardized for example data obtained by using a standardised procedure, or better still, data obtained from experiments carried out in the same laboratory, to reduce systematic errors that would arise between different laboratories.

5.1.2. Cancer Risk Coefficient

An attempt has been made to express risk in terms of the new system of dosimetry i.e. by using ABE (see section 4.4.1). The ICRP results for risk (cancer) assessment are used for this purpose (see section 3.3.1.8). In the future for application in operational radiological protection, BE values which are considered as an upper limit in a certain period such as in a year, and the limit for a lifetime, have to be set.

5.1.3. The Proposed New Dosimetry System

5.1.3.1. General

The new dosimetry system as explained in chapter four is thought to be more rigorous and meaningful. It is superior in many aspects compared to the conventional system, such as:

i. The ABE values for various radiations are more consistent and provide smoother curves (refer to fig. 4.4) compared to Q (refer to table 1.5) or w_R values (refer to table 1.6) of radiation (i.e. less smooth curve and as a step function); and

ii. The derivation of ABE is based directly on experimental radiobiology interpreted in terms of the basic radiation physics. Consequently it is more meaningful than the derivation of Q and w_R.

There are many implications of having a better system of dosimetry. More precise dosimetry is desirable in operational plants such as a nuclear power plant or an irradiation facility, because it means:

a. precise allocation of job in controlled or very high radiation areas. From economic point of view, this will save operational cost of the plant due to

maximum utilisation of the available man-power;

b. radiation workers, management staff as well as regulator staff will know the amount of radiation received more precisely. From legal point of view, this will facilitate them in complying with the existing legal requirements i.e. rules and regulations.

5.1.3.2. Damage due to Neutrons, Heavy Ions, Photons and Electrons

In the conventional dosimetry system, neutrons are considered to be most damaging i.e. w_R=20, in the energy range between 100 keV to 2 MeV (see table 1.6). For alpha particles and heavy ions, w_R= 20 for all energies and for electrons w_R=1 for all energies. From the published data where the inactivation cross-section P is plotted against λ [149], it has been found that neutrons are just able to reach the saturation region and the P decreases for lower λ. Alpha particles are comparable with neutrons. However heavy ions are capable to be in the saturation region with maximum P about up to three times the saturation inactivation cross-section. On the basis of these facts, in the new system, neutrons can not be as damaging as heavy ions but the most damaging heavy ions and neutrons will differ by a factor of three. The maximum damage of alpha particles and neutrons are about the same. On the same basis electrons are found to be less damaging by at least an order of magnitude and hardly can reach the saturation region.

The damaging soft photon energy is considered to be due to the λ of the relevant charged particle fluence being in the order of 2 nm. However its penetration is limited due to its range R. In this region the factor R/d, where d is the diameter of the cell nucleus, is playing a significant role, although λ is about 2 nm but R/d is near to zero.

The inactivation cross section P, of gamma, is an order of magnitude lower than for heavy ions. The possible explanation for this is due to the penetration capability of the secondary charged particles produced by gamma (i.e. secondary electrons). At their most damaging, they are not able to penetrate through the cell nucleus whereas the heavy ions do, at the same λ.

5.1.3.3. Incorporated Radionuclides

As pointed out by Younis et-al [53] the conventional system may not suitable for assessing the hazard from incorporated radionuclides due to:

i. Many of radionuclides have complex decay schemes, accompanied by auger electron cascades, which have ranges localised in cellular or sub-cellular dimensions thereby producing a large degree of damage; or

ii. If the radionuclide is incorporated into an especially sensitive site within the cell structure, excessive damage may be expected.

In the new system the concept of fluence is applicable. It takes care of the charged particles produced by the incorporated radionuclides.

Improved risk control presented in this thesis is given in terms of the absolute biological effectiveness (ABE). Here, the term absolute means the ability to define the biological effect uniquely, in terms of fundamental physical and biological quantities. The new dosimetry system proposed has distinct advantages over the existing system:

i. the calculation of ABE is based on the DNA dsb, which is directly related to various end-points of prime importance in radiological protection;

ii. It is additive in nature, so that the BE of a radiation field is a direct mixture of BE of the relevant charged particle fluence;

iii. Knowing the BE value for a given radiation field, the risk associated can be assessed without the need to know the radiation type and quantity;

iv. ABE is a unified measure of quality making other modifying factors such as Q or w_R redundant;

v. The values reflect the probability of cancer induction in one lifetime after receiving the radiation exposure; and

vi. If an instrument which measures the BE directly can be designed and made available, the BE values received by individuals during a specified period can be measured and the risks associated with the exposure can be determined.

5.2. Recommendations For Future Work

For the new dosimetry system, the ABE values presented in this work may be further improved by:

i. Using the efficiency factor ε, against λ obtained from experimental data. By doing so all uncertainties in deriving the efficiency factor ε, can be minimised (see section 4.2.1 and 4.3.2); and

ii. The factor R/d, (i.e. to correct for insider tracks having range R less than cell diameter, d) may be applied more accurately to the lower energy interval of the relevant (equilibrium) charged particle fluence generated in the medium.

The overall risk (cancer) assessment can be carried out in terms of ABE. Data from the Japanese epidemiological study may be used. In order to do that the following is required;

i. BE value for each individual, instead of individual dose, can be evaluated;

ii. A complete set of ABE values against energies for gamma and neutrons and their respective fluence;

iii. By using the same cohorts (see section 3.1.1.6), assess the risk in term of BE by using the same methods and procedures i.e. apply multiplicative or relative projection models;

If the cancer risk is expressed in terms of BE, a value of risk can be set, as acceptable for radiological protection purpose. By assuming linear relationship between risk and BE, maximum value of BE can be set for radiation workers and members of the public annually.

In order to apply the new dosimetry system, instrumentation to measure BE is required. Basically in its design concept has to incorporate the sensitive sites separated in 2 nanometre distance (i.e. an array of sensitive sites). The inactivation (or events) of the pair of sensitive sites spaced at 2 nm distance, is registered and the number recorded corresponds to the exposure received. Many possible types of detectors can be investigated in the future such as using organic macro-molecules and phosphors in solid phase. An active research programme to achieve such detectors is supported by the Commission of the European Communities.

The role of a hormesis effect in low, near environmental levels of radiation, as reported in the literature has to be investigated not just because of its intrinsic importance but because of its relevance to test of models. The hormesis effect (or adaptation effect) [150] is defined as the induction of beneficial effects by low doses of an otherwise harmful physical or chemical agent including radiation. Fremlin [151] has concluded that the most probable explanation for hormesis is in the education of the immune system, which is very complex and is capable of learning to deal with a variety of threats to living cells. It is however a controversial issue because it is not supported by statistical analysis. There is also evidence that low dose radiation increases metastasis of some tumours. Fabrikant as mentioned by Sugahara et-al [152] made a case for a DDREF for humans in the range of 3 to 4 rather than 2 which is used both by ICRP (No 60) and BEIR V committee (NAS). In future, when sufficient data is available this controversial issue may be resolved.

Finally, it is believed that the unified dosimetry system, which has been presented in this thesis, is able to provide an improved system of damage limitation for better risk control in radiological protection near environmental level. Success in devising appropriate measuring instruments would ensure the application of the new dosimetry system in operational radiological protection.

Appendix One

Programme photonabef.for, to calculate ABE for Photon

```
c       Program 'photonabef.for' calculates ABE for various energy x and
c       gamma in keV. ABE iscalculated by taking into account the
c       electron spectra generated  per unit incident x or gamma fluence.
c       This program include mean free path for equilibrium electron spectrum.
        implicit none
        real*8 eng(100), gsig(100), dsig,
        1d, r(100), fl(100), abeg(100), mfp(100)
        Integer n, le, ndp
        open(unit=30,status='old',access='sequential',file='gh2o2f.dat')
        open(unit=48,status='unknown',access='sequential',file='photonabef.dat')
        n=15
        dsig=4.0e-08
        d=6.0e-04
c       dsig is the DNA geometrical cross section given in cm2.
c       d is the mean chord length of the cell nucleus as 6 microns,
c       but given in cm (6 micron= 6.0e-04 cm)
        read(30,10)
10      format(a)
        read(30,*) ndp
        do 150 le=1,ndp
        read(30,*) eng(le),gsig(le),fl(le),r(le),mfp(le)
150     continue
c       fluence fl(le) has already incorperated efficiency factor
c       =(1-exp(-2/lamda).
        write(48,155)
155     format(1h ,2x,'Gamma Energy',5x,'ABE for Gamma',5x,'mean free path
nm')
        do 250 le=1,ndp
        abeg(le)=dsig*n*fl(le)*gsig(le)
        write(48,255) eng(le),abeg(le),mfp(le)
255     format(1h ,5x,1pe10.2,5x,1pe10.2,5x,1pe10.2)
250     continue
        stop
        end
```

Input Data for Program photonabef.for

File: gh2o2f.dat (ecfrl.crs)
Number of data points: 31

Photon Energy	Cross Section	Fluence	Range	mfp λ
0.277	3.200E+04	6.8302E-07	3.57E-07	3.35E+00
0.392	2.576E+04	1.0821E-06	4.75E-07	3.41E+00
0.849	6.107E+03	8.2969E-07	3.73E-07	3.38E+00
1.486	1.422E+03	3.1117E-06	1.54E-06	3.97E+00
3.310	1.421E+02	9.6100E-06	9.80E-05	5.81E+00
5.410	3.245E+01	1.7030E-05	5.93E-05	7.89E+00
5.900	2.489E+01	1.8620E-05	5.00E-05	8.00E+00
6.400	1.939E+01	2.0388E-05	4.17E-05	8.81E+00
6.925	1.520E+01	2.2223E-05	4.88E-05	9.26E+00
8.040	9.570E+00	2.5867E-05	6.48E-05	1.01E+01
8.630	7.674E+00	2.7872E-05	7.57E-05	1.05E+01
9.880	5.026E+00	3.1747E-05	9.25E-05	1.11E+01
10.53	4.107E+00	3.3801E-05	1.02E-04	1.14E+01
11.21	3.381E+00	3.5618E-05	1.17E-04	1.17E+01
11.900	2.808E+00	3.7673E-05	1.29E-04	1.19E+01
14.140	1.634E+00	4.2980E-05	1.72E-04	1.18E+01
15.750	1.159E+00	4.6183E-05	2.08E-04	1.16E+01
17.440	8.334E-01	4.8817E-05	2.30E-04	1.09E+01
22.100	3.870E-01	5.1890E-05	3.13E-04	9.09E+00
23.110	3.351E-01	5.2111E-05	3.17E-04	8.70E+00
27.380	1.961E-01	4.9986E-05	3.46E-04	7.61E+00
32.060	1.224E-01	4.6165E-05	3.49E-04	6.94E+00
39.910	6.832E-02	3.9421E-05	3.36E-04	6.62E+00
50.390	4.179E-02	3.4618E-05	2.89E-04	6.94E+00
58.830	3.295E-02	3.3967E-05	2.63E-04	7.41E+00
59.600	3.240E-02	3.4113E-05	2.63E-04	7.51E+00
68.130	2.816E-02	3.5919E-05	2.53E-04	8.12E+00
76.250	2.607E-02	3.8924E-05	2.65E-04	8.77E+00
97.000	2.469E-02	5.1089E-05	3.52E-04	1.06E+01
661.000	3.255E-02	8.9335E-04	3.59E-02	6.31E+01
1253.300	2.974E-02	3.1818E-03	1.20E-01	1.04E+02

Programme neutronabe.for, to calculate ABE for Neutron

```
c       Program `neutronabe.for` calculates ABE for neutrons
c       with various energies. ABE is calculated by adding the ABE of
c       hydrogen recoils and ABE of oxygen recoils generated per unit
c       incident neutron fluence.
        implicit none
      real*8 eneut(100), flh(100), flo(100),
        1mfph(100), mfpo(100), nsigh(100),
        2nsigo(100), dsig, abeh(100), abeo(100), aben(100), d, rh(100),
        3ro(100)
        Integer nh, no, le, ndp
        open(unit=30,status='old',access='sequential',file='nh2o4.dat')
        open(unit=48,status='unknown',access='sequential',file='
        1neutronabe.dat')
        nh=15
        no=15
        dsig=4.0e-08
        d=6.0e-04
c       d is the mean chord length of the cell nucleus, taken as 6 micron.
c       dsig is the DNA geometrical cross section.
        read(30,10)
10      format(a)
        read(30,*) ndp
        do 150 le=1,ndp
        read(30,*) eneut(le),nsigh(le),nsigo(le),flh(le),flo(le),
        1mfph(le),mfpo(le),rh(le),ro(le)
150     continue
        write(48,155)
155     format(1h ,2x,'Neutron Energy',5x,'ABE Neutrons',2x,'mfp H',5x,
        1'mfp O')
        do 250 le=1,ndp
```

```
c       epsilh(le)=(1-exp(-2/mfph(le)))
c       epsilo(le)=(1-exp(-2/mfpo(le)))
c       rdh(le)=rh(le)/d
c       if (rdh(le).gt.1) rdh(le)=1
c       abeh(le)=dsig*rdh(le)*nh*flh(le)*epsilh(le)*nsigh(le)
        abeh(le)=dsig*nh*flh(le)*nsigh(le)
c       rdo(le)=ro(le)/d
c       if (rdo(le).gt.1) rdo(le)=1
c       abeo(le)=dsig*rdo(le)*no*flo(le)*epsilo(le)*nsigo(le)
        abeo(le)=dsig*no*flo(le)*nsigo(le)
        aben(le)=abeh(le)+abeo(le)
c       nsigh has incorporated the effect of two hydrogen atom
c       per water molecule, in its value.
c       Note: in this calculation R/d factor is not applied to the
c       average values for ABE calculation. It has to be applied
c       to each fractions of the spectrum in the main programme.
        write(48,255) eneut(le),aben(le),mfph(le),mfpo(le)
255     format(1h ,5x,1pe10.2,5x,1pe10.2,5x,1pe10.2,5x,1pe10.2)
250     continue
        stop
        end
```

The Input file nh2o4.dat: Number of data points: 63.

Neutron En	$N\sigma_H$	$N\sigma_O$	$Fluence_H$	$Fluence_O$	mfp λ_H	mfp λ_O	Range -H	Range-O
1.000E-01	1.368E+00	1.300E-01	7.828E-07	3.157E-09	3.114E+01	9.828E-08	2.493E-03	5.381E-04
1.500E-01	1.367E+00	1.300E-01	1.151E-06	5.267E-09	2.386E+01	1.257E-07	3.099E-03	6.396E-04
2.000E-01	1.367E+00	1.300E-01	1.501E-06	7.116E-09	1.965E+01	1.398E-07	4.128E-03	7.262E-04
3.000E-01	1.365E+00	1.300E-01	2.164E-06	1.032E-08	1.488E+01	1.536E-07	6.585E-03	8.745E-04
4.000E-01	1.364E+00	1.300E-01	2.790E-06	1.311E-08	1.222E+01	1.602E-07	9.156E-03	1.002E-03
5.000E-01	1.363E+00	1.300E-01	3.390E-06	1.562E-08	1.049E+01	1.640E-07	1.173E-02	1.117E-03
6.000E-01	1.361E+00	1.300E-01	3.959E-06	1.795E-08	9.290E+00	1.668E-07	1.422E-02	1.222E-03
7.000E-01	1.361E+00	1.300E-01	4.515E-06	2.012E-08	8.377E+00	1.686E-07	1.669E-02	1.320E-03
8.000E-01	1.359E+00	1.300E-01	5.040E-06	2.219E-08	7.687E+00	1.705E-07	1.901E-02	1.414E-03
9.000E-01	1.358E+00	1.300E-01	5.558E-06	2.414E-08	7.113E+00	1.717E-07	2.135E-02	1.503E-03
1.000E+00	1.357E+00	1.300E-01	6.056E-06	2.603E-08	6.653E+00	1.732E-07	2.356E-02	1.588E-03
1.500E+00	1.351E+00	1.300E-01	8.344E-06	3.456E-08	5.170E+00	1.787E-07	3.388E-02	1.975E-03
2.000E+00	1.344E+00	1.300E-01	1.037E-05	4.215E-08	4.357E+00	1.837E-07	4.307E-02	2.321E-03
3.000E+00	1.337E+00	1.297E-01	1.395E-05	5.551E-08	3.466E+00	1.924E-07	5.916E-02	2.939E-03
4.000E+00	1.328E+00	1.297E-01	1.702E-05	6.769E-08	2.974E+00	2.013E-07	7.314E-02	3.502E-03
5.000E+00	1.322E+00	1.297E-01	1.979E-05	7.901E-08	2.658E+00	2.100E-07	8.564E-02	4.028E-03
6.000E+00	1.313E+00	1.297E-01	2.224E-05	8.975E-08	2.433E+00	2.184E-07	9.714E-02	4.529E-03
7.000E+00	1.306E+00	1.293E-01	2.453E-05	9.985E-08	2.266E+00	2.263E-07	1.077E-01	5.015E-03
8.000E+00	1.294E+00	1.293E-01	2.656E-05	1.098E-07	2.134E+00	2.344E-07	1.178E-01	5.485E-03
9.000E+00	1.282E+00	1.293E-01	2.840E-05	1.195E-07	2.030E+00	2.427E-07	1.271E-01	5.947E-03
1.000E+01	1.278E+00	1.293E-01	3.031E-05	1.289E-07	1.943E+00	2.505E-07	1.361E-01	6.391E-03
1.500E+01	1.236E+00	1.287E-01	3.788E-05	1.733E-07	1.668E+00	2.891E-07	1.759E-01	8.560E-03
2.000E+01	1.190E+00	1.283E-01	4.358E-05	2.149E-07	1.522E+00	3.270E-07	2.103E-01	1.060E-02
3.000E+01	1.129E+00	1.277E-01	5.303E-05	2.945E-07	1.372E+00	4.041E-07	2.698E-01	1.462E-02
4.000E+01	1.069E+00	1.270E-01	5.987E-05	3.700E-07	1.300E+00	4.812E-07	3.222E-01	1.848E-02
5.000E+01	1.026E+00	1.260E-01	6.589E-05	4.428E-07	1.263E+00	5.593E-07	3.702E-01	2.236E-02

Neutron En	$N\sigma_H$	$N\sigma_O$	$Fluence_H$	$Fluence_O$	mfp λ_H	mfp λ_O	Range -H	Range-O	
6.000E+01	9.824E-01	1.253E-01	7.067E-05	5.149E-07	1.241E+00	6.393E-07	4.155E-01	2.622E-02	
7.000E+01	9.423E-01	1.247E-01	7.474E-05	5.850E-07	1.228E+00	7.183E-07	4.594E-01	3.000E-02	
8.000E+01	9.022E-01	1.240E-01	7.796E-05	6.540E-07	1.219E+00	7.975E-07	5.018E-01	3.378E-02	
9.000E+01	8.688E-01	1.227E-01	8.113E-05	7.183E-07	1.214E+00	8.720E-07	5.441E-01	3.759E-02	
1.000E+02	8.360E-01	1.223E-01	8.372E-05	7.878E-07	1.211E+00	9.542E-07	5.850E-01	4.144E-02	
1.500E+02	7.084E-01	1.190E-01	9.487E-05	1.107E-06	1.222E+00	1.353E-06	7.983E-01	6.015E-02	
2.000E+02	6.282E-01	1.166E-01	1.059E-04	1.415E-06	1.259E+00	1.782E-06	1.026E+00	7.873E-02	
3.000E+02	5.253E-01	1.213E-01	1.287E-04	2.135E-06	1.374E+00	2.932E-06	1.561E+00	1.141E-01	
4.000E+02	4.411E-01	4.144E-01	1.461E-04	9.475E-06	1.513E+00	1.433E-05	2.186E+00	1.480E-01	
4.400E+02	4.244E-01	2.654E-01	1.565E-04	6.611E-06	1.573E+00	1.040E-05	2.464E+00	1.611E-01	
5.000E+02	3.983E-01	1.247E-01	1.709E-04	3.474E-06	1.667E+00	5.792E-06	2.923E+00	1.796E-01	
6.000E+02	3.622E-01	9.692E-02	1.949E-04	3.168E-06	1.830E+00	5.798E-06	3.759E+00	2.099E-01	
7.000E+02	3.342E-01	9.358E-02	2.192E-04	3.492E-06	1.996E+00	6.968E-06	4.668E+00	2.387E-01	
8.000E+02	3.101E-01	9.692E-02	2.434E-04	4.051E-06	2.166E+00	8.773E-06	5.675E+00	2.666E-01	
9.000E+02	2.920E-01	1.738E-01	2.700E-04	8.007E-06	2.339E+00	1.872E-05	6.777E+00	2.927E-01	
1.000E+03	2.760E-01	1.738E-01	2.969E-04	8.727E-06	2.516E+00	2.196E-05	7.990E+00	3.179E-01	
1.500E+03	2.219E-01	6.684E-02	4.364E-04	4.630E-06	3.405E+00	1.576E-05	1.515E+01	4.327E-01	
2.000E+03	1.885E-01	4.679E-02	5.838E-04	4.025E-06	4.317E+00	1.738E-05	2.442E+01	5.320E-01	
3.000E+03	1.504E-01	7.286E-02	9.012E-04	8.401E-06	6.144E+00	5.161E-05	4.821E+01	7.038E-01	
3.750E+03	1.276E-01	7.854E-02	1.114E-03	1.057E-05	7.540E+00	7.968E-05	7.103E+01	8.157E-01	
4.000E+03	1.223E-01	6.016E-02	1.191E-03	8.460E-06	8.006E+00	6.771E-05	7.950E+01	8.505E-01	
5.000E+03	1.043E-01	4.278E-02	1.484E-03	6.995E-06	9.853E+00	6.890E-05	1.167E+02	9.833E-01	
6.000E+03	9.089E-02	3.228E-02	1.773E-03	5.952E-06	1.172E+01	6.974E-05	1.609E+02	1.103E+00	
7.000E+03	8.086E-02	2.774E-02	2.064E-03	5.655E-06	1.360E+01	7.688E-05	2.114E+02	1.216E+00	
8.000E+03	7.218E-02	2.156E-02	2.333E-03	4.786E-06	1.550E+01	7.418E-05	2.693E+02	1.320E+00	
9.000E+03	6.549E-02	2.326E-02	2.602E-03	5.571E-06	1.738E+01	9.676E-05	3.313E+02	1.421E+00	
1.000E+04	6.282E-02	3.275E-02	3.004E-03	8.389E-06	1.926E+01	1.614E-04	3.993E+02	1.518E+00	

Neutron En	$N\sigma_H$	$N\sigma_O$	$Fluence_H$	$Fluence_O$	mfp λ_H	mfp λ_O	Range -H	Range-O	
1.500E+04	4.277E-02	4.545E-02	4.229E-03	1.503E-05	2.884E+01	4.324E-04	8.334E+02	1.948E+00	
2.000E+04	3.208E-02	5.514E-02	5.319E-03	2.187E-05	3.842E+01	8.364E-04	1.400E+03	2.334E+00	
3.000E+04	2.038E-02	5.080E-02	7.086E-03	2.612E-05	5.796E+01	1.501E-03	2.958E+03	3.029E+00	
4.000E+04	1.490E-02	4.478E-02	8.762E-03	2.792E-05	7.754E+01	2.137E-03	5.008E+03	3.692E+00	
5.000E+04	1.149E-02	3.910E-02	1.006E-02	2.850E-05	9.594E+01	2.688E-03	7.416E+03	4.343E+00	
6.000E+04	9.156E-03	3.409E-02	1.102E-02	2.845E-05	1.136E+02	3.167E-03	1.015E+04	5.017E+00	
7.000E+04	7.619E-03	3.041E-02	1.205E-02	2.862E-05	1.313E+02	3.671E-03	1.335E+04	5.708E+00	
8.000E+04	7.418E-03	2.740E-02	1.483E-02	2.881E-05	1.486E+02	4.170E-03	1.683E+04	6.441E+00	
9.000E+04	7.218E-03	2.473E-02	1.784E-02	2.871E-05	1.664E+02	4.640E-03	2.087E+04	7.173E+00	
1.000E+05	7.017E-03	2.273E-02	2.098E-02	2.897E-05	1.842E+02	5.167E-03	2.531E+04	7.949E+00	

Neutron Cross Section

Neutron Cross Sections are arranged according to Neutron Energy. Neutron Cross-section (hydrogen) $(Nsig)_H$ and Neutron Cross-section (oxygen) $(Nsig)_O$. Number of data points is 63.

Neutron Energy.	$(Nsig)_H$.	$(Nsig)_O$
1.00E-01,	20.470,	3.890
1.50E-01,	20.460,	3.890
2.00E-01,	20.450,	3.890
3.00E-01,	20.430,	3.890
4.00E-01,	20.410,	3.890
5.00E-01,	20.400,	3.890
6.00E-01,	20.370,	3.890
7.00E-01,	20.360,	3.890
8.00E-01,	20.340,	3.890
9.00E-01,	20.320,	3.890
1.00E+00,	20.310,	3.890
1.50E+00,	20.210,	3.890
2.00E+00,	20.110,	3.890
3.00E+00,	20.000,	3.880
4.00E+00,	19.870,	3.880
5.00E+00,	19.780,	3.880
6.00E+00,	19.640,	3.880
7.00E+00,	19.540,	3.870
8.00E+00,	19.370,	3.870
9.00E+00,	19.190,	3.870
10.00E+00,	19.130,	3.870
15.00E+00,	18.500,	3.850
20.00E+00,	17.800,	3.840
30.00E+00,	16.900,	3.820
40.00E+00,	16.000,	3.800
50.00E+00,	15.350,	3.770
60.00E+00,	14.700,	3.750

Neutron Energy、 $(Nsig)_H$ 、 $(Nsig)_O$		
70.00E+00、	14.100、	3.730
80.00E+00、	13.500、	3.710
90.00E+00、	13.000、	3.670
100.00E+00、	12.510、	3.660
150.00E+00、	10.600、	3.560
200.00E+00、	9.400、	3.490
300.00E+00、	7.860、	3.630
400.00E+00、	6.600、	12.400
440.00E+00、	6.350、	7.940
500.00E+00、	5.960、	3.730
600.00E+00、	5.420、	2.900
700.00E+00、	5.000、	2.800
800.00E+00、	4.640、	2.900
900.00E+00、	4.370、	5.200
1.00E+03、	4.130、	5.200
1.50E+03、	3.320、	2.000
2.00E+03、	2.820、	1.400
3.00E+03、	2.250、	2.180
3.75E+03、	1.910、	2.350
4.00E+03、	1.830、	1.800
5.00E+03、	1.560、	1.280
6.00E+03、	1.360、	0.966
7.00E+03、	1.210、	0.830
8.00E+03、	1.080、	0.645
9.00+03、	0.980、	0.696
1.00E+04、	0.940、	0.980
1.50E+04、	0.640、	1.360
2.00E+04、	0.480、	1.650
3.00E+04、	0.305、	1.520
4.00E+04、	0.223、	1.340

Neutron Energy、 $(Nsig)_H$ 、	$(Nsig)_O$
5.00E+04、 0.172、	1.170
6.00E+04、 0.137、	1.020
7.00E+04、 0.114、	0.910
8.00E+04、 0.111、	0.820
9.00E+04、 0.108、	0.740
1.00+05、 0.105、	0.680

Appendix Two

Derivations of the Linear Energy Transfer (LET) values and the Absolute Biological Effectiveness (ABE) values (refer to table 4.4 page 172) used in expressing risk in terms of the unified dosimetry system are as follows:

A.1. For hydrogen recoil

(Refer to table 3(a) page 7-8 [144])

For neutron energy E_n=300 keV, L=64.11

E_n=1500 keV, L=$3.961\times10^{+01}$

E_n=2000 keV, L=$3.365\times10^{+01}$

For E_n=1600 keV, L=$3.9661\times10^{+01}$+(33.65-39.61)x100/500 = 38.42.

A.2. For oxygen recoil

(Refer to table 3(b) page 9-10 [144])

For neutron energy E_n=300 keV, L=$2.005\times10^{+02}$

E_n=1500 keV, L=$2.564\times10^{+02}$

E_n=2000 keV, L=$2.755\times10^{+02}$

For E_n=1600 keV, L=256.4+(275.5-256.4)x100/500 = 260.22

A.3. Effective LET for neutron L_{eff}

Effective LET for neutron L_{eff}, is calculated by averaging L of all recoils generated per unit incident neutron fluence, by using the following formula:

$$L_{eff} = f_H.L_{T,H} + f_O.L_{T,O}$$

where,

- f_H is the fraction of hydrogen recoil fluence to the total fluence (i.e. ϕ_H / ϕ_{H+O});
- $L_{T,H}$ is track average LET due to hydrogen recoil;
- f_O is the fraction of oxygen recoil fluence to the total fluence (i.e. ϕ_O / ϕ_{H+O}); and
- $L_{T,O}$ is track average LET due to oxygen recoil.

For neutron energy E_n=300 keV,

ϕ_H=1.287X10^{-04}; and

ϕ_O = 2.135X10^{-06}.

Therefore:

L_{eff}={1.287X10^{-04}/(1.287X10^{-04}+2.135X10^{-06})}x64.11

+{2.135X10^{-06}/(1.287X10^{-04}+2.135X10^{-06})}x2.005x10^{-02}

L_{eff}=66.34

For neutron energy E_n=1600 keV,

ϕ_H=4.750x10^{-04}; and

ϕ_O=4.440x10^{-06}.

Therefore: L_{eff}={4.750X10^{-04}/(4.750X10^{-04}+4.440X10^{-06})}x38.42

+{4.440X10^{-06}/(4.750X10^{-04}+4.440X10^{-06})}x260.22

L_{eff}=40.47

A.4. LET For Gamma-rays

(Refer to table 3(a) [142])

For gamma energy E_γ=1253.3 keV, L=0.306

E_γ=661 keV, L=0.475

For E_γ=1000 keV: L=0.475 + (0.306-0.475)X(1000-661)/(1253.3-661)= 0.378

B.1. Derivation of ABE for gamma

ABE values for gamma can be obtained fron the graph shown in figure 4.2.

For gamma energy E_γ=1000 keV, from the graph ABE_{1000}=3.75E-11.

B.2. Derivation of ABE for Neutron

For neutron the ABE values can be obtained from the graph shown in figure 4.3 (refer to page 162). From the graph;

For neutron energy E_n=300 keV, ABE_{300}=3.95E-11; and

For neutron energy E_n=1600 keV, ABE_{1600}=6.06E-11.

References

[1] NCRP 1993 Limitation of Exposure to Ionizing Radiation NCRP Report No. 116 National Council on Radiation Protection and Measurements Bathesda Maryland pp 8-11.

[2] Cember H 1983 Introduction to Health Physics (2nd. Edition) Pergamon Press Oxford pp 177-199.

[3] Lovell S 1979 An Introduction to Radiation Dosimetry Cambridge University Press pp 102-112.

[4] Hall E J 1978 Radiobiology for the Radiologist (2 nd. Edition) Harper & Row London pp 31-62.

[5] Fry R J M Ullrich R L 1986 Combined Effects of Radiation and Other Agents in Radiation Carcinogenesis (Edited by A C Upton R E Albert F J Burns R E Shore) Elsevier London pp 437-454.

[6] Gonzalez A J 1994 Biological Effects of Low Doses of Ionizing Radiation: A Fuller Picture Special Report *IAEA Bulletin* **4**/1994.

[7] Shapiro J 1981 Radiation Protection A Guide for Scientists and Physicians (2 nd Edition) Harvard University Press London pp 324-419.

[8] Kadiri L A 1990 Dosimetry for Absolute Biological Effectiveness of Ionising Radiations Ph.D Thesis University of St. Andrews UK.

[9] Dietze G Siebert B R L 1994 Photon and Neutron Dose Contributions and Mean Quality Factors in Phantoms of Different Size Irradiated by Monoenergetic Neutrons *Radiation Research* **140** 130-133.

[10] Watt D E Alkharam A S Child M B Salikin M S 1994 Dose as a Damage Specifier in Radiobiology for Radiation Protection Letters to the editor of Radiation Research *Radiation Research* **139** 249-251.

[11] Katz R 1994 Commentary: Dose *Radiation Research* **137** 410-413.

[12] Katz R Hofmann W 1984 Some Comments on the Concepts of Dose and Dose Equivalent *Health Physics* **47** 4 603-611.

[13] Katz R 1994 Reply to D E Watt A S Alkharam M B Child and M S Salikin Dose as a Damage Specifier in Radiobiology for Radiation Protection A Comment on Dose *Radiation Research* **139** 251-253.

[14] Bond V P Varma M N Sondhaus C A Feinendegen L E 1985 An Alternative to Absorbed Dose Quality and RBE at Low Exposures *Radiation Research* **104** s-52-s-57.

[15] Simmons J A 1992 Absorbed Dose- An Irrelevant Concept for Irradiation with Heavy Charged Particles? *J. Radiol. Prot.* **12** 3 173-179.

[16] Attix F H 1986 Introduction to Radiological Physics and Radiation Dosimetry Wiley-Interscience Publication New York pp 1-37.

[17] ICRU 1993 Stopping Powers and Ranges for Protons and Alpha Particles ICRU Report 49 International Commission on Radiation Units and Measurements Bathesda Maryland.

[18] Evans R D 1968 x-Ray and γ ray interactions in Radiation Dosimetry (Second Edition Vol 1 Fundamental) Academic Press London pp 94-153.

[19] Roesch W C and Attix F H 1968 Basic Concepts of Dosimetry in Radiation Dosimetry (Second Edition Vol 1 Fundamental) Academic Press London pp 1-40.

[20] Alpen E L 1990 Radiation Biophysics Prentice-Hall Inc. the USA pp 74-90.

[21] Burlin T E 1972 Vacuum Chambers for Radiation Measurement in Topics in Radiation Dosimetry Supplementary 1 Edited by Attix Academic Press London pp 143-220.

[22] Personal communication with Dr. Watt D E.

[23] ICRU 1971 Radiation Quantities and Units ICRU Report 19 International Commission on Radiation Units and Measurements Washington D.C.

[24] Chilton A B 1978 A note on the Fluence Concept *Health Physics* **34** 715-718.

[25] Chilton A B 1979 Further Comments on An Alternate Definition of Fluence *Health Physics* **36** 637-638.

[26] ICRU 1980 Radiation Quantities and Units ICRU Report 33 International Commission on Radiation Units and Measurements Bathesda Maryland.

[27] ICRU 1970 Linear Energy Transfer ICRU Report 16 International Commission on Radiation Units and Measurements Washington D.C.

[28] Watt D E Al-Kazwini A T Al- Shaibani H M A and Twaiz D A A 1981 Studies in Enzyme Inactivation as a Prelude to Damage Modelling in Proceeding of 7th Symposium on Microdosimetry Oxford 1980 EUR 7147 (Edited by J Booz H D Hartfield and H G Ebert) Harwood Academic Publisher pp 1475-1488.

[29] Attix F H 1986 Introduction to Radiological Physics and Radiation Dosimetry John Wiley & Sons Inc. New York pp 501-504.

[30] Rossi H H 1968 Microscopic Energy Distribution in Irradiated Matter in Radiation Dosimetry (Second Edition) Academic Press London pp 43-90.

[31] ICRU 1983 Microdosimetry ICRU Report 36 International Commission on Radiation Units and Measurements Bathesda Maryland.

[32] Zaider M Rossi H H 1986 Microdosimetry and Its Application to Biological Processes Plenum Press New York pp 171-238.

[33] ICRP 1977 Recommendations of the International Commission on Radiological Protection ICRP Publication 26 Annals of the ICRP **1**(3) Pergamon Press Oxford.

[34] ICRP 1990 1990 Recommendations of the International Commission on Radiological Protection ICRP Publication 60 Annals of the ICRP 21 Pergamon Press Oxford.

[35] Sinclair W K 1992 Radiation Protection: Recent Recommendations of the ICRP and the NCRP and Their Biological Basis in Advances in Radiation Biology Vol. 16 (Edited by O F Nygaard W K Sinclair J T Lett) Academic Press London pp 303-324.

[36] ICRP 1985 Statement from the 1985 Paris Meeting of the International Commission on Radiological Protection in Quantitative Bases for Developing a Unified Index of Harm ICRP Publication 45 Annals of the ICRP 15(3) Pergamon Press Oxford pp i-ii.

[37] Clarke R H 1989 Current Estimates of Radiation Risks and Implications for Dose Limits in Radiation Protection Theory and Practice (Edited by E P Goldfinch) IOP Publishing Ltd Bristol pp 31-36.

[38] ICRP 1977 Problems Involved in Developing an Index of Harm ICRP Report 27 Annals of the ICRP 1(4) Pergamon Press Oxford pp 12-16.

[39] Booz J Feinendegen L E 1988 A microdosimetric understanding of low dose radiation effects *Int. J. Radiat. Biol.* **53**(1) pp 13-21.

[40] UNSCEAR 1986 1986a Genetic and Somatic Effects of Ionising Radiation Annex B Dose Response Relationships for Radiation Induced Cancer United Nations Scientific Committee on the Effects of Atomic Radiation E.86.1X.9 United Nations New York.

[41] Goodhead D T 1990 Radiation Effects in Living Cells *Can. J. Phys.* **68** 872.

[42] Alberts A Bray D Lewis J Raff M Roberts K Watson J D 1983 Molecular Biology of the Cell Garland Publishing Inc. London pp 98-111.

[43] Frankenberg D Frankenberg-Schwager M Harbich R 1984 Interpretation of the shape of survival curves in terms of induction and repair-mis-repair of DNA double strand breaks *Br. J. Cancer* **49** Suppl. VI 233.

[44] Natarajan A T Obe G Van Zeeland A A Palitti F Meijers M Verdegaal-Immerzeel E A M 1980 Molecular mechanisms involved in the production of chromosomal aberrations. II Utilization of Neurospora endonuclease for the study of aberration production by X-rays in G1 and G2 stages of the cell cycle *Mutation Research* **69** 293.

[45] Ward J F 1988 DNA Damage Produced by Ionizing Radiation in Mammalian Cells: Identities Mechanisms of Formation and Reparability *Progress in Nucleic Acid Research and Molecular Biology* **35** 95-125.

[46] Ward J F 1990 The Yield of DNA double-strand breaks Produced intracellularly by Ionising Radiation A Review *Int. J. of Radiat. Biol.* **57** 1141-1150.

[47] Watt D E 1992 Letter to Editor: Comment on Mechanism of Radiation Effects with Special Reference to Transformation *Int. J. Radiat. Biol.* **61** 2 263-267.

[48] Liniecki J 1989 Cancer Risk Coefficient for High Doses and Dose Rates and Extrapolation to the Low Dose Domain in The Effects of Small Doses of Radiation IBC Technical Services Ltd. London.

[49] Sumner D Wheldon T Watson W 1991 Radiation Risks (3 rd. Edition) Antony Rowe Ltd. Chippenham pp 87-127.

[50] Martin E A (Editor) 1990 Concise Medical Dictionary (3 rd. Edition) Oxford University Press Oxford pp 98.

[51] ICRP 1985 Quantitative Bases for Developing a Unified Index of Harm ICRP Publication 45 Annals of the ICRP **15** No.3 Pergamon Press Oxford.

[52] Howell R W Narra V R Sastry K S R Rao D V 1993 On the Equivalent Dose for Auger Electron Emitters *Radiation Research* **134** 71-78.

[53] Younis A R S Watt D E 1989 The Quality of Ionizing Radiations Emitted by Radionuclides Incorporated Into Mammalian Cells *Phys. Med. Biol.* **34** 7 821-834.

[54] Humm J L Chin L M 1993 A Model of Cell Inactivation by Alpha-Particle Internal Emitters *Radiation Research* **134** 143-150.

[55] Pienta K J Coffey D S 1984 A Structural Analysis of the Role of the Nuclear Matrix and DNA Loops in the Organization of the Nucleus and Chromosome *J. Cell Sci.* Suppl.**1** 123-135.

[56] Puck T T Marcus P I 1956 Action of X-rays On Mammalian Cells *J. Exp. Med.* **103** pp 653-666.

[57] Dertinger H Jung H Zimmer K G 1969 Molecular Radiation Biology Heidelberg Science Library Vol.12 Springer-Verlag Berlin pp 1-23.

[58] Todd P 1966 Medical College of Virginia Quarterly 1 pp 2-14.

[59] Wideroe R 1966 High energy electron therapy and the two component theory of radiation *Acta Radiol.* **4** 257-278.

[60] Neary G J 1965 Chromosome aberrations and the theory of RBE 1. General considerations *Int. J. Rad. Biol.* **9** 477.

[61] Zimmer K G 1961 Studies on Quantitative Radiation Biology Oliver and Boyd London pp 9-64.

[62] Lea D E 1946 Actions of Radiations on Living Cells Cambridge Univ Press London.

[63] Kappos A Pohlit W 1972 A cybernetic model for radiation reactions in living cells I. Sparsely ionizing radiations; stationary cells *Int. J. Radiat. Biol.* **22** 51.

[64] Goodhead D T 1985 Saturable repair models of radiation action in mammalian cells *Radiation Research Suppl.* 8 **104** s-58.

[65] Barendsen G W 1964 Impairment of the proliferative capacity of human cells in culture by α-particles with differing linear-energy transfer *Int. J. Radiat. Biol.* **8** 453

[66] Barendsen G W 1979 Influence of radiation quality on the effectiveness of small doses for induction of reproductive death and chromosome aberrations in mammalian cells *Int. J. Radiat. Biol.* **36** 49.

[67] Curtis S B 1991 Application of the LPL model to Mixed Radiations in Biophysical Modelling of Radiation Effects (Edited by KH Chadwick G Moschini M N Varma) Adam Hilger Bristol pp 21-28.

[68] Chadwick K H Leenhouts H P 1981 The molecular Theory of Radiation Biology Springer Verlag Heidelberg.

[69] Zaider M 1991 The Application of the principle of "Dual Radiation Action" in Biophysical Modelling in Biophysical Modelling of Radiation Effects (Edited by KH Chadwick G Moschini MN Varma) Adam Hilger Bristol pp 37-45.

[70] Goodhead D T 1987 Biophysical Models of Radiation Action: Introductory Review in Proceeding of the 8th. International Congress of Radiation Research Edinburgh July 1987 (Edited by E M Fielden J W Fowler J H Hendry and D Scott) Taylor and Francis London pp 306-311.

[71] Chadwick K H Leenhouts H P 1981 The Molecular Model for Cell Survival Following Radiation in The Molecular Theory of Radiation Biology Springer-Verlag New York pp 25.

[72] Kellerer A M Rossi H H 1972 The Theory of Dual Radiation Action *Current Topics in Radiation Research Quarterly* vol. viii pp 85-158.

[73] Kellerer A M Rossi H H 1978 A Generalized Formulation of Dual Radiation Action *Radiation Research* **75** 471.

[74] Paretzke H G 1991 Biophysical Models of Radiation Action-Development of Simulation Codes in Nato ASI Series H54 The Early Effects of Radiation on DNA (Edited by E M Fielden and P O'Neil Springer-Verlag Berlin Heidelberg pp 17-31.

[75] Varma M N Bond V P 1988 Hit Size Effectiveness Approach in Biophysical Modelling in Quantitative Mathematical Models in Radiation Biology in Proceedings of the Symposium at Schloss Rauisch-Holzhausen FRG (Edited by J Kiefer) Springer-Verlag Berlin pp 119-124.

[76] Ostashevsky 1993 Cell Recovery Kinetics for Split-Dose. Multi-fractionated and Continuous Irradiation in the DSB Model *Int. J. Radiat. Biol.* **63** 1 47-58.

[77] Hall E J 1991 Biophysical Models in Radiation Biology in Biophysical Modelling of Radiation Effects (Edited by K H Chadwick G Moschini M N Varma) Adam Hilger Bristol pp 1-11.

[78] Curtis S B 1986 Lethal and Potentially Lethal Lesions Induced by Radiation- A Unified Repair Model *Radiation Research* **106** 252-270.

[79] Curtis S B 1987 The cellular consequences of Binary Misrepair and Linear Fixation of Initial Biophysical Damage in Proceeding of the 8th International Congress of Radiation Research Edinburgh, July 1987 (Edited by E M Fielden J F Fowler J H Hendry and D Scott) Taylor and Francis London pp 312-317.

[80] Curtis S B 1982 Ideas on the Unification of Radiobiological Theories in the 8th. Symposium on Microdosimetry (Edited by J Booz H G Ebert) pp 527-536.

[81] Tobias C A Blakely E A Ngo F Q H and Yang T C H 1980 The Repair-Misrepair Model of Cell Survival in Radiation Biology in Cancer Research (Edited by R A Meyn and H R Withers) Raven Press New York pp 195- 230.

[82] Curtis S B 1988 The Lethal and Potentially Lethal Model- A Review and Recent Development in Quantitative Mathematical Models in Radiation Biology in Proceedings of the Symposium at Schloss Rauisch-Holzhausen FRG (Edited by J Kiefer) Springer-Verlag Berlin pp 138-146.

[83] Curtis S B 1991 Application of the LPL model to mixed radiations in Biophysical Modelling of Radiation Effects (Edited by K H Chadwick G Moschini M N Varma) Adam Hilger Bristol pp 21-28.

[84] Iliakis G Bryant P E Ngo F Q H 1985 Independent Forms of Potentially Lethal Damage Fixed in Plateau-Phase Chinese Hamster Cells by Post-irradiation Treatment in Hypertonic Salt Solution or araA *Radiation Research* **104** 329-345.

[85] Iliakis G Ngo F Q H Roberts W K Youngman K 1985 Evidence for Similarities between Radiation Damage Expressed by β-araA and Damage Involved in the Interaction Effect Observed after Exposure of V79 Cells to Mixed Neutrons and γ Radiation *Radiation Research* **104** 303-316.

[86] Barendsen G W Beusker T L J Vergroesen A J Budke L 1960 Effects of different Ionizing Radiations on Human Cells in Tissue Culture 11. Biological Experiments *Radiation Research* **13** 841.

[87] Raju M R Jett J H 1974 RBE and OER Variations of Mixtures of Plutonium Alpha Particles and X-rays for Damage to Human Kidney Cells (T-1) *Radiation Research* **60** 473.

[88] Ngo F Q H Blakely E A Tobias C A 1981 Sequential Exposures of Mammalian Cells to Low- and High-LET Radiations 1. Lethal Effects Following X-ray and Neon-Ion Irradiation *Radiation Research* **87** 59.

[89] Virsik R P Blohm R Hermann K P Modler H and Harder D 1983 Chromosome aberrations and the mechanism of "primary lesion interaction" in Eighth Symposium in Microdosimetry (Edited by J Booz and H G Ebert) publisher pp 409-422.

[90] Harder D 1987 Pairwise Lesion Interaction- Extension and Confirmation of LEA's Model in Proceeding of the 18 th. International Congress of Radiation Research (Edited by Fielden E

M Fouler J F Henry J H Scott D vol. 2) Taylor and Francis London pp 318-324.

[91] Harder D 1988 The Pairwise Lesion Interaction Model in Quantitative Mathematical Models in Radiation Biology in Proceeding of the Symposium at Schloss Rauisch-Holzhausen FRG (Edited by J Kiefer) Springer-Verlag Berlin pp 159-170.

[92] Harder D Virsik-Peuckert R P Bartels E R 1994 Theory of Intra-track Pairwise Lesion Interaction *Radiation Protection Dosimetry* **52** 1-4 13-16.

[93] Harder H Virsik-Peuckert P Bartels E 1992 Theory of Pairwise Lesion Interaction in Biophysical Modelling of Radiation Effects (Edited by K H Chadwick G Moschini M N Varma) Adam Hilger Bristol pp 179-184.

[94] Virsik R P Harder D 1982 Effects of L-cysteine on the dose effect relationship for chromosomal aberrations in irradiated human lymphocytes *Int. J. Radiat. Biol.* **42** 211-214.

[95] Katz R Sharma S C Homayoonfar M 1972 The Structure of Particle Tracks. In Topics in Radiation Dosimetry. Suppl. 1 (Edited by F H Attix) Academic Press New York pp 317-383.

[96] Katz R Ackerson B Homayoonfar M Sharma S C 1971 Inactivation of Cells by Heavy Ion Bombardment *Radiation Research* **47** 402-425.

[97] Katz R 1988 Radiobiological Modelling Based On Track Structure in Quantitative Mathematical Models in Radiation Biology in Proceedings of the Symposium at Schloss Rauisch-Holzhausen FRG (Edited by J Kiefer) Springer-Verlag Berlin pp 57-83.

[98] Katz R Dunn D E Sinclair G L 1985 Thindown in Radiobiology *Radiation Protection Dosimetry* **13** 1-4 281-284.

[99] Goodhead D T 1989 Relationships of radiation track structure to biological effect: A re-interpretation of the parameters of the Katz model *Nucl. Tracks Radiat. Meas.* **16** 2/3 177-184.

[100] Waligorski P R Olko P 1991 Are Neutron Data Unsuitable for Making Model Predictions of Radiation Risk? in Biophysical Modelling of Radiation Effects (Edited by K H Chadwick G Moschini M N Varma) Adam Hilger Bristol pp 125-136.

[101] Skarsgard L D, Kihlman B A, Parker L, Pujara A M and Richardson S 1967 Survival, Chromosome Abnormalities, and Recovery in Heavy- Ion- and X-Irradiated Mammalian Cells *Radiation Research* Supplement 7 208-221.

[102] Yang T C, Craise L M, Mei M T, and Tobias C A 1985 Neoplastic Cell Transformation by Heavy Charged Particles *Radiation Research* **104** s-177-s-187.

[103] Underbrink A G Huczkowski J Woch B Gedlek E Cebulska-Wasilweska A Litwinniszyn M Kasper E 1978 Institute of Nuclear Phys. Krakow Report 1039/B.

[104] Waligorski M P R Morstin K Bond V P Baum J W 1990 Analysis of Biological Effectiveness of Heavy Ions Using Two Microdosimetric Approaches *Radiation Protection Dosimetry* **31** 1/4 303-307.

[105] Bond V P 1986 Influence of Dose Rate and LET in Radiation Carcinogenesis: Theory and Observations in Radiation Carcinogenesis (Edited by A C Upton R E Albert F J Burns R E Shore) Elsevier London pp 413-436.

[106] Bond V P Varma M N 1982 A Stochastic Weighted Hit Size Theory of Cellular Radiobiological Action in Proceedings of the Eight Symposium in Microdosimetry EUR 8395 pp 423-437.

[107] Bond V P 1981 The Conceptual Basis for Evaluating Risk from Low -Level Radiation Exposure in Critical Issues in Setting Radiation Protection Dose Limits Proceedings of the 17th Annual Meeting NCRP April 8-9.

[108] Weber K J 1988 Models of Cellular Radiation Action - An Overview in Quantitative Mathematical Models in Radiation Biology in Proceedings of the Symposium at Schloss Rauisch-Holzhausen FRG (Edited by J Kiefer) Springer-Verlag Berlin pp 3-27.

[109] Sparrow A H Underbrink A G Rossi H H 1972 Mutations induced in Tradescantia by small doses of X-rays and neutrons: Analysis of dose response curves *Science* **176** 916-921.

[110] Nauman C H Underbrink A G Sparrow A H 1975 Influence of radiation dose rate on somatic mutation induction in tradescantia stamen hairs *Radiation Research* **62** 79-96.

[111] Underbrink A Kellerer A Mills R Sparrow A 1976 Comparison of X-ray and gamma ray dose response curves for pink somatic mutations in Tradescantia clones 02 *Rad. Environ. Biophys.* **13** 295-303.

[112] Skarsgard L D Kihlman B A Parker L Pujara C M Richardson S 1967 Survival chromosome abnormalities and recovery in heavy ion and X-irradiated mammalian cells *Radiation Research Suppl.*7 208-221.

[113] Watt D E Kadiri L A Glodic S 1991 Observed cellular effects lead to a track 'core' model of radiation action in Biophysical Modelling of Radiation Effects (Edited by K H Chadwick G Moschini M N Varma) Adam Hilger New York pp 201-209.

[114] Watt D E 1994 Heavy Particle Track Structure Parameters for Biophysical Modelling Nuclear Instrument and Methods in Physics Research B **93** 215-221.

[115] Cannell R J Watt D E 1985 Scientific note Biophysical mechanisms of damage by fast ions to mammalian cells in vitro *Phys. Med. Biol.* **30** 3 255-258.

[116] Chen C Z Watt D E 1986 Biophysical mechanism of radiation damage to mammalian cells by x and γ-rays *Int. J. Radiat. Biol.* **49** 131-142.

[117] Hall E J Bedford J S 1964 Dose Rate: its Effect on the Survival of HeLa Cells Irradiated with Gamma Rays *Radiation Research* **22** 308-315.

[118] Hill C K Buonaguro F M Myers C P Han A Elkind M M 1982 Fission Spectrum Neutrons at Reduced Dose Rates Enhance Neoplastic Transformation *Nature* **298** 67-69.

[119] Hill C K Han A Elkind M M 1984 Fission Spectrum at a Low Dose Rate Enhance Neoplastic Transformation in the Linear Low Dose Region (0-10 cGy) *Int. J. Radiat. Biol.* **46** 11-15.

[120] Hieber L Ponsel G Roos H Venn S Fomke E Kellerer A M 1987 Absence of a Dose-rate Effect in the Transformation of C3H10T1/2 Cells by Alpha Particles *Int. J. Radiat. Biol.* **52**(6) 859-869.

[121] Eguchi-Kasai K Murakami M Itsukaichi H Fukutsu K Kanai T Furusawa Y Sato K Ohara H and Yatagai F 1994 The Role of DNA Repair on Cell Killing by Charged Particles. Submitted to *Advances in Space Research.*

[122] Miller R C Pehrson G R Hieber L Marino S A Richards M Hall E J 1993 The Inverse Dose-Rate Effect for Oncogenic Transformation by Charged Particles is Dependent on Linear Energy Transfer *Radiation Research* **133** 360-364.

[123] ICRP 1977 Problems Involved in Developing An Index of Harm ICRP Report 27 Annals of The ICRP Pergamon Press Oxford **1** 4 1977 pp 12-14.

[124] Storer J B 1096 Carcinogenic Effects: An Overview; in Radiation Carcinogenesis Edited by Upton A C Albert R E Burns F J Shore R E Elsevier Science Publishing Co. Inc. London pp 11-21.

[125] Coppola M 1991 How to model radiation carcinogenesis in Biophysical Modelling of Radiation Effects (Edited by K H Chadwick G Moschini M N Varma) Adam Hilger New York pp 339-342.

[126] Bryant P E Riches A C 1989 Short Communication: Oncogenic Transformation of Murine C3H 10T1/2 Cells Resulting from DNA Double Strand Breaks Induced by a Restriction Endonuclease *Br. J. Cancer* **60** 852-854.

[127] Mayneord W V Clarke R H 1975 Carcinogenesis and Radiation Risks: A Biomathematical Reconnaissance British Journal of Radiology Supplement Number 12 The British Institute of Radiology pp 1-10.

[128] Thiessen J W Kaul D C 1991 The Dosimetry System 1986 (DS86) and the Tentative Dosimetry System 1965 (T65D): How Do They Compare, What is Left to Do? *J. Radiat. Res., Supplement* 1-10.

[129] Bishop J M 1987 The Molecular Genetics of Cancer *Science* **235** pp 305-311.

[130] Lambert B E 1989 The Underlying Biology of Radiation Carcinogenesis in the Effects of Small Doses of Radiation IBC Technical Services Ltd. London.

[131] Dennis J A 1994 Risk Assessment is a Hazardous Business *Radiation Protection Dosimetry* **55** 4 243-245.

[132] Watt D E 1989 On Absolute Biological Effectiveness and Unified Dosimetry *J. Radiol. Prot.* **9** 1 33-49.

[133] Bryant P E 1989 Restriction Endonuclease- and Radiation-Induced DNA Double-Strand Breaks and Chromosomal Aberrations: Similarities and Differences in Chromosomal Aberrations Basic and Applied Aspects (Edited by G Obe and A T Natarajan) Springer-Verlag Berlin Heidelberg pp 61-69.

[134] Watt D E 1989 An Approach Towards A Unified Theory of Damage to Mammalian Cells by Ionising Radiation for Absolute Dosimetry *Radiation Protection Dosimetry* **27** 2 73-84.

[135] Watt D E Kadiri L A 1990 Physical Quantification of the Biological Effectiveness of Ionizing Radiations *International Journal of Quantum Chemistry* Vol. **xxxviii** 501-520.

[136] Watt D E Al-Affan I A M Chen C Z Thomas G E 1985 Identification of Biophysical Mechanisms of Damage by Ionizing Radiation *Radiation Protection Dosimetry* **13** 1-4 285-294.

[137] Watt D E Kadiri L A Glodic S 1991 Observed Cellular Effects Lead to a Track Core Model of Radiation Action in Biophysical Modelling of Radiation Effects (Edited by K H Chadwick G Moschini M N Varma) Adam Hilger Bristol pp 201-209.

[138] Watt D E Chen C Z Kadiri L and Younis A 1988 Paper 6. Towards A Unified System for Expression of Biological Damage by Ionising Radiation in Health Effects of Low Dose Ionising Radiation BNES London pp 37-41.

[139] Watt D E 1988 Absolute Biological Effectiveness of Neutrons and Photons *Radiation Protection Dosimetry* **23** 1/4 63-67.

[140] Joint Evaluated File Library. JEF-PC version 1.0 1994 Centre de Spectrometrie Nucleaire et de Spectrometrie de Masse, CSNSM, IN2P3-CNRS, Batiment 108, F-91405 Orsay Campus, France.

[141] Watt D E 1989 Track Structure Data for Ionising Radiations in Liquid Water Part 1: Electrons and Photons, University of St. Andrews, St. Andrews, Scotland KY16 9TS Report Biophys/10/89.

[142] Watt D E 1993 Track Structure Data for Ionising Radiations in Liquid Water Part 2: Heavy Charged Particles, 100 eV to 1 GeV, University of St. Andrews, St. Andrews, Scotland KY16 9TS, Report Biophys/1/93.

[143] Watt D E 1993 Track Structure Data for Ionising Radiations in Liquid Water Part 3: Monoenergetic neutrons 0.5 keV to 100 MeV, University of St. Andrews, St. Andrews, Scotland KY16 9TS, Report Biophys/11/93 [Revised Jan 1995].

[144] Maruyama T 1986 Atomic Bomb Dosimetry for Epidemiological Studies of Survivors in Hiroshima and Nagasaki in GANN Monograph on Cancer Research no.32 (Edited by I Shigematsu A Kagan) Plenum Press London pp 9-28.

[145] Christy R F Tajima E 1987 Executive Summary in US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki Vol.1 RERF pp 14-25.

[146] Jin T Watt D E Kobayashi K 1994 Damage Induced by Monochromatic Synchrotron x-Rays at the Resonance Absorption Energy of Intracellular Phosphorous in Yeast Cells *Appl. Radiat. Isot.* **45** 7 767-772.

[147] Sykes C E Watt D E 1989 Interpretation of the increase in the frequency of neoplastic transformations observed for some ionising radiations at low dose rates *Int. J. Radiat. Biol.* **55** 6 925-942.

[148] Spadinger I Palcic B 1992 Technical Report: Cell Survival Measurements at Low Doses Using An Automated Image Cytometry Device *Int. J. Radiat. Biol.* **63** 2 183-189.

[149] Watt D E Alkharam A S 1994 Charged Particle Track Structure Parameters for Application in Radiation Biology and Radiation Chemistry *Int. J. Quantum Chemistry: Quantum Biology Symposium* **21** 195-207.

[150] Dennis J A 1994 Hormesis or Adaptation *Radiation Protection Dosimetry* **3** 155-156.

[151] Fremlin J H 1989 Radiation Hormesis in the Effects of Small Doses of Radiation IBC Technical Services Ltd. London.

[152] Sugahara T Sagan L A and Aoyama T 1992 'Low dose irradiation and biological defence mechanisms' Elsevier Science Publishers, Netherlands.

Index